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SILICATES

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SUMMARY

Description Silica and the silicates from sources that are likely to be candidates for human intake occur in a number of different forms -- 30 to 40 as a rough estimation. They exhibit a range of solubilities and of crystalline or noncrystalline forms. Generally speaking most are assumed to be somewhat soluble from the surface area in the juices of the gastrointestinal tract.

Occurrence In the natural environment, silicon occurs in practically all forms of plant, animal, and sea life (262). It is in all natural waters: mineral water, hot springs, city water, well-water and sea water (006). Also, it has been found in the atmosphere in the vicinity of factories manufacturing silicon and its alloys (147). As a food additive, up to 2% may be incorporated in a given food (018,019,020 and 021). Average daily intakes have been estimated as 481 mg for calcium silicate, 340 mg for silica serogel, 2278 mg for sodium aluminum silicate, and 2.66 mg for sodium calcium aluminosilicate hydrate (375).

Acute Toxicity Lethal Dose (LD) values (from various forms of silica) of from 9 mg/kg BW (194) to 150 mg/kg BW (209) for mice by the intravenous route have been reported. Intraperitoneally, from 50 mg/kg BW to 250 mg/kg for silica sol (209) and 4250 mg/kg

for talc administered to mice are recorded. LD values for rats range from 35.2 mg/kg (084) to 100 mg/kg (209) i.v., intratracheally 30 and 50 mg/kg (397), and intraperitoneally 100 mg/kg for these animals (397).

For guinea pigs i.p. 100 (397) and 120 to 240 mg/kg (209), and i.v. 100 mg/kg (209) are recorded. Rabbits given i.v. injections succumbed to doses from 35 to 141 mg/kg (209), cats from 15 to 193 mg/kg (348), and dogs intragastrically 25-50 cc of colloidal silicic acid (476) and i.v. 20 mg/kg of particulate silica (260). In humans, fatal cases from talc aspiration (351), and talc embolism from i.v. injections by drug addicts (043,542) have been reported.

Short Term Studies

Short term studies on rats have shown positive weight-gain effects (061) with no toxic effects from diatomaceous earth of large particle size. Weight-gain effects were variable for rats fed various forms of commercial silicic acid preparations (273). Precipitated amorphous silica (of particle size 19-25 mu) administered intratracheally to rats (084) resulted in lung lesions. Silicates; alumium, sodium or magnesium, along with silicon dioxide gave only mild clinical symptoms of polydipsia and polyuria when fed to rats, with no drug-related lesions noted (372). Dogs, however, treated similarly (372) showed gross

and microscopic renal lesions from the sodium and magnesium silicates, but none with alumium silicate or silicon dioxide. Guinea pigs administered a variety of talc samples i.p. showed a fibrosis reaction similar to the foreign body reaction (441). Children exposed to low atmospheric concentrations of silicon dioxide (147) evidenced an increased morbidity rate and a definite lag in general physical development.

Long Term Studies

Rabbits given 2% suspensions of quartz, (176) of particle size 1 to 3 μ and 6 to 12 μ, and aluminum oxide 1 to 3 μ, after 2 to 3 years showed accumulation of the silica particles in different locations according to their size. The largest were found in the pulmonary capillaries, intermediate size in the spleen and hepatic lymph node and the finest ones in the liver. The fine particles were the most active producing nodular cirrhosis of the liver. Coarse particles were less irritating, exciting a simple foreign body reaction which progressed very little in three years. Aluminum oxide particles were merely phagocytosed and produced no fibrosis. A human long term study (006) utilizing slides of the aorta of Japanese patients (known to have a high silica content from talc milled rice in their diet) showed silica in the aorta walls, in the adventitia layer increasing with age, in the intima layer decreasing with age and in the media

remaining constant. At age 40 to 42, the contents of the adventitia and intima layers reversed, perhaps related to hypertension in arteriosclerosis.

Biochemistry

In rats (084,273,511) silica in various forms and in varying amounts was accumulated in body tissue, primarily the liver and spleen in the case of oral administration; the lungs, liver and spleen, when given intratracheally; and the lungs, liver, spleen and kidneys, when given i.v. In the case of colloidal silica administered i.p. there was accumulation of polymerized silica in particle form found in the kidney tubules (041). In the case of humans taking magnesium trisilicate as antiacid for extended periods renal calculi with high silica content have been reported (302). A numerical estimation of excretion for rats fed chronic doses (511) showed fecal excretion in the range of 95% of the administered dose, 4% as urinary excretion and 1% accumulated in the tissue. When the silica enters the body through the lungs a considerable amount is caught in the capillary bed of the lungs, some remaining there and some progressively moving to storage sites in other organs (084). When given i.v. the lungs act as a filter for silica particles (359). Renal lesions have definitely been attributed to silica compounds of colloidal particle size (398, 399). Blood protein fractions, histamine (186), and

blood lipids (481) have been notably affected by both crystalline and amorphous silica. Finally, the silica taken up by the macrophages reacts with the membranes surrounding the secondary lysosomes, releasing lytic enzymes into the cytoplasm (012).

Carcinogenicity

Both diatomaceous earth (475) and talc (342) have been shown to produce stomach lesions -- the former in Sherman rats, a rare finding in animals; and the latter in humans on high talc milled rice diet. Also, there are numerous cases of internal granulomas, at times fatal from talc used in surgical procedures (139,213). Locally, widespread granulomata were found as a result of continued heavy use of talcum powder after bathing (496).

Teratology

Colloidal silica (Ludox^{R}) has been shown to produce retarded lid development or exopthalmia, encephalocele or exencephaly, external edematous blebs, ectopic viscera, retarded feathering and crossed or short upper beak in chick embryos injected in the amniotic cavity (526).

Epidemiology

A high goiter incidence in the high Valle of Aosta (Spain) was attributed to high silica content of the natural water due to runoff from the mountainous and volcanic slopes (493). Also, endemic nephropathy caused by rock erosion in village communities on the banks of the lower reaches of large rivers has been

reported (329).

Consumer Exposure

The approximate high possible daily intake for the 2-65 year old age group has been estimated by the NAS/NRC GRAS survey to be:

calcium silicate: 481 mg

silica aerogel: 340 mg

sodium aluminum silicate: 2278 mg

sodium calcium aluminosilicate: 2.66 mg

The WHO/FAO monograph on "Toxicological Evaluation of Some Food Colors, Emulsifiers, Stabilizers, and Anti-Caking Agents and Certain Other Substances" (165) set no limit on Acceptable Daily Intakes for the various forms of silicon dioxide, aluminum silicate, calcium silicate, magnesium silicate (including talc) and sodium alumino silicate.

CHEMICAL INFORMATION

I. Nomenclature

Silica (SiO_2) from a number of different sources, and in a number of different forms, is a component of human intake. Forms likely to be assimilated as food additives, and some pure forms occurring in nature which are possible candidates for human intake, are described chemically in Table 1. Throughout this monograph the biological studies described will be considered from the standpoint of the silica, with the form initially administered being specified, when known.

In addition to the forms listed in Table 1, other classifications of silica compounds are considered in the monograph. Oligosilicic acid is a term used to described mono and lower silicic acids; polysilicic acid refers to the higher, protein-precipitating forms (194). Condensed silicic acids such as disilicic acid ($H_6Si_2O_7$) and trisilicic acid ($H_4Si_3O_8$) occur in rocks which through reaction with the metals therein and by weathering may find their way into the water-supply (262). Diatomaceous earth consists of the siliceous skeletons of the microscopic plant life of the sea - the Diatom. They form the most important food of aquatic animal life (262). This skeleton, or shell, is made up of silica chemically combined with organic and mineral substances (Al, Fe, Ca, Mg, K, Na, H_3PO_4), or the silica may be adhered to a membrane of the Diatom (244). Kahane and Antoine (244), believe that silica participates in a metabolizing system, a state of circulation, before becoming a constituent of the shell of the Diatom, and call this "constitu-

tional silica". The contrasting form, by these authors' definitions, is "interposed silica" which is external in orgin and plays its role mechanically as a foreign body.

II. Empirical Formula

See Table 1.

III. Structural Formula

Not Included.

IV. Molecular Formula

See Table 1.

Table 1

Silica Compounds that may be Components of Human Intake *

Common Name	Chemical Name	Formula	Molecular Wt	Description	Melting Point	Solubility
Muscovite	Aluminum Potassium Silicate	$3Al_2O_3 \cdot K_2O \cdot 6SiO_2 \cdot 2H_2O$	796.40	Monoclinic	Decomposes	Insoluble in cold water
Orthoclase	Aluminum Potassium Silicate	$Al_2O_3 \cdot K_2O \cdot 6SiO_2$	556.49	Colorless, monoclinic	1450°C	Insoluble in cold water
Microcline	Aluminum Potassium Silicate	$Al_2O_3 \cdot K_2O \cdot 6SiO_2$	556.49	Colorless, triclinic	1150°C	Insoluble in cold water
Sillimanite	Aluminum Silicate	Al_2SiO_5	162.00	White, rhombic	1860°C	Insoluble in cold and hot water and in alkali
	Aluminum Silicofluoride	$Al_2(SiF_6)_3$	480.12	White powder		Soluble in hot water, slightly soluble in cold
Zeolex (Trade name)	Aluminum Sodium Silicate	$Al_2O_3 \cdot Na_2O \cdot 6SiO_2$	524.29	Colorless, triclinic	1100°C	Insoluble in cold and hot water, soluble in dilute acid
Diopside	Calcium Magnesium Silicate	$CaO \cdot MgO \cdot 2SiO_2$	216.52	White, monoclinic	1391°C	Insoluble in hot and cold water
Pseudowollastonite	Calcium Silicate (α)	$CaSiO_3$	116.14	Colorless, pseudohexagonal	1540°C	Very slightly soluble in cold water, soluble in HCl

Common Name	Chemical Name	Formula	Molecular Wt	Description	Melting Point	Solubility
Wollastonite	Calcium Silicate (β)	$CaSiO_3$	116.14	Colorless, monoclinic	Transition to α form at 1190°C	
	Calcium Silicide	$CaSi_2$	96.20			Insoluble in cold water, decomposes in hot water
	Calcium Silicofluoride	$CaSiF_6$	182.14	Colorless		Slightly soluble in cold water, decomposing; soluble in HCl, HF and alkali.
	Calcium Silicofluoride (hydrate)	$CaSiF_6 \cdot 2H_2O$	218.17	White, tetragonal		Decomposes in cold water, soluble in H_2SiF_6
	Iron Silicide	FeSi	83.91	Yellow-gray, octagonal		Insoluble in hot and cold water, and in aquea regia
Talc	Magnesium Silicate	$Mg_3Si_4O_{11} \cdot H_2O$	379.22	White, monoclinic or rhombic		Insoluble in hot and cold water, and in alkali.
	Magnesium Silicide	Mg_2Si	76.70	Slate blue, cubic	1102°C	Decomposes in cold water and in HCl
	Magnesium Silicide	Mg_5Si_3	205.78		1102°C	Insoluble in cold water; decomposes in hot water, alkali and NH_4Cl

Common Name	Chemical Name	Formula	Molecular Wt	Description	Melting Point	Solubility
	Magnesium Silicofluoride	$MgSiF_6 \cdot 6H_2O$	274.48	Colorless, trigonal	Decomposes	Soluble in hot and cold water.
	Potassium Silicate	K_2SiO_3	154.25	Hygroscopic	976°C	Soluble in cold and hot water, insoluble in alkali
	Potassium Tetrasilicate	$K_2Si_4O_9 \cdot H_2O$	352.45	Rhombic	Decomposes at 400°C	Soluble in cold and hot water, insoluble in alkali
Hieratite	Potassium Silicofluoride	K_2SiF_6	220.25	Colorless, hexagonal or cubic	Decomposes	Very slightly soluble in cold and hot water; soluble in HCl; insoluble in alkali and NH_3
Silica Gel	Metasilicic acid	H_2SiO_3	78.08	Amorphous		Insoluble in hot and cold water; soluble in alkali; insoluble in NH_4Cl
Silica Sol	Orthosilicic acid	H_4SiO_4	96.09	Amorphous		Slightly soluble in cold and hot water; soluble in alkali; insoluble in NH_4Cl
	Silicon, crystalline	Si	28.06	Gray, cubic	1420°C, B.P.2600°C	Insoluble in hot and cold water; soluble in HNO_3, HF, Ag; slightly soluble in Pb, Zn; insoluble in HF.

Common Name	Chemical Name	Formula	Molecular Wt	Description	Melting Point	Solubility
	Silicon, graphitic	Si	28.06	Crystalline	B.P.2600°C	Insoluble in cold and hot water, soluble in HNO_3, HF, fused alkali; insoluble in HF
	Silicon, amorphous	Si	28.06	Brown, amorphous	B.P.2600°C	Insoluble in hot and cold water; soluble in HF, KOH
Opal	Silicon Dioxide	$SiO_2 \cdot xH_2O$		Iridescent, amorphous	1600-1750°C sublimates	Insoluble in hot and cold water; soluble in HF, hot alkali, fused $CaCl_2$
Cristobalite	Silicon Dioxide	SiO_2	60.06	Colorless, cubic or tetragonal	1710°C, B.P.2230°C	Insoluble in hot and cold water; soluble in HF; insoluble in alkali
Lechateli-erite	Silicon Dioxide	SiO_2	60.06		B.P.2230°C	Insoluble in hot and cold water; soluble in HF; insoluble in alkali
Quartz	Silicon Dioxide	SiO_2	60.06	Hexagonal	Transition <1425 B.P.2230°C	Insoluble in hot and cold water; soluble in HF; insoluble in alkali
Tridymite	Silicon Dioxide	SiO_2	60.06	Trigonal, rhombic	Transition 1670°C	Insoluble in cold water; soluble in

Common Name	Chemical Name	Formula	Molecular Wt	Description	Melting Point	Solubility
					B.P.2230°C	HF: insoluble in alkali
Silica Gel, (Trade name)	Silicon Dioxide, hydrate	$3SiO_2 \cdot H_2O$	198.20	White, amorphous	$-H_2O$ at 1200°C	Very slightly soluble in hot and cold water
	Sodium Metasilicate	Na_2SiO_3	122.05	Colorless, rhombic	1088°C	Soluble in cold water, soluble and decomposes in hot water, insoluble in Na or K salts and alkali
	Sodium Metasilicate (hydrate)	$NaSiO_3 \cdot 9H_2O$	284.20	Rhombic	47°C, $-6H_2O$ at 100°C	Very soluble in hot and cold water; soluble in .5 N NaOH
	Sodium Orthosilicate	Na_4SiO_4	184.05	Colorless, hexagonal	1018°C	Soluble in hot and cold water
	Sodium Silicate	$Na_2Si_4O_9$	302.23	Amorphous		Soluble in hot and cold water, insoluble in Na or K salts and alkali
	Zinc Silicate	$ZnSiO_3$	141.44	Hexagonal or rhombic	1437°C	Insoluble in cold water
	Zinc Silicofluoride	$ZnSiF_6 \cdot 6H_2O$	315.54	Colorless, hexagonal	Decomposes	Soluble in cold and hot water.

* Data extracted from Lange's Handbook of Chemistry.

V. Specifications

A. Aluminum Sodium Silicate (Zeolex)

1. FDA specifications, data supplied by them.

	Procedure: Codex
Silicon Dioxide:	**Not less than 66%, not more than 71% of SiO_2 after drying.**
Al_2O_3:	**Not less than 9%, not more than 13% of Al_2O_3 after drying.**
Na_2O:	**Not less than 5%, not more than 6% of Na_2O after drying.**
Loss on drying:	**Not more than 8%**
Heavy Metals:	
Arsenic as As	**Not more than 3 ppm (0.0003%)**
Heavy Metals (as Pb)	**Not more than 10 ppm (0.001%)**

Must meet Codex specification.

2. **Food Use - Commercial specifications (data supplied by the FDA).**

Color and Appearance	White Powder.
Granulation	
On USBS Sieve #100	0.2% Maximum.
On USBS Sieve #200	0.5% Maximum.
On USBS Sieve #325	1.0% Maximum.
Moisture	9.0% Maximum
Odor	Clean, free from objectionable odors.
pH	10.0 ± 1.0
Visual Impurities	None

B. **Calcium Silicate**

1. **Commercial specifications - Technical Grade for industrial use only (paint, rubber and plastics industries). Data supplied by the FDA.**

CALCIUM SILICATE (1) $3CaO \cdot 3SiO_2$

Item	Typical Analysis	Specification
SiO_2	66%	
CaO	19%	
NaCl	1.43%	2.0% max.
Loss at 105°C.	2.1%	6.0% max.
Ignition Loss above 105°C.	9.7%	
R_2O_3	0.7%	
MgO	0.2%	
Cu and Mn (Total)	0.004%	
As	1 ppm	
Hg	< 0.1 ppm	
Pb	6 ppm	
F	40 ppm	
Heavy Metals as Lead	15 ppm	

2.

CALCIUM SILICATE (2) $CaO \cdot 12SiO_2$

Item	Typical Analysis	Specification
SiO_2	80%	83% max.
CaO	4.0%	7% max.
NaCl	1.0%	2% max.
Loss at 105°C.	6.0%	3-9%
Ignition Loss above 105°C.	8.0%	8% max.
Fe_2O_3	0.13%	0.20% max.
Al_2O_3	0.45%	1% max.
R_2O_3	0.60%	
As	0.3 ppm	1 ppm max.
Hg	0.1 ppm	1 ppm max.
Pb	8 ppm	10 ppm max.
F	7 ppm	50 ppm max.
Heavy Metals as Lead	25 ppm	25 ppm max.

C. **Silicon Dioxide**

1. **Commercial specifications, for industrial use in the rubber and plastics industries. Data supplied by the FDA.**

SILICA - HYDRATED, PRECIPITATED

Item	Typical Analysis	Specifications
SiO_2 (dry basis)	94%	87.0% minimum
pH in 5% Water Suspension	7.0%	6.5 - 7.3
Loss at 105°C.	5.3%	3.0 - 7.0%
NaCl	1.7%	
CaO	0.80%	
R_2O_3	0.63%	
Combined Cu and Mn	0.003%	
As	0.5 ppm	
Hg	< 0.5 ppm	
Pb	5 ppm	
Heavy Metals as Pb	15 ppm	

2. **Food Use - as a conditioning agent - commercial specification. Data supplied by the FDA.**

SILICON DIOXIDE

Color and Appearance	White powder.
Moisture	1.5% Maximum.
Odor	Clean, free from objectionable odors.
pH	3.9 ± 0.4
Visual Impurities	None.
Loss on Ignition	3.0% Maximum.
Bulk Density, Tapped	0.071 ± 0.006

3. Food Chemicals Codex, 1972 Edition (104).

Description

Silica aerogel is a white, fluffy, powdered or granular microcellular silica. Hydrated silica is a precipitated, hydrated silicon dioxide occurring as a fine, white, amorphous powder, or as beads or granules. Both forms of silicon dioxide are insoluble in water and in alcohol and other organic solvents, but are soluble in hot phosphoric or hydrofluoric acids and in solutions of alkalies at 80° to 100°.

Specifications

Assay

Silica aerogel: Not less than 90.0% of SiO_2.

Hydrated silica: Not less than 89.0% of SiO_2, calculated on the dried basis.

Loss on drying. Hydrated silica: not more than 6%.

Loss on ignition. Not more than 6%.

Limits of Impurities

Arsenic (as As). Not more than 3 parts per million (0.0003%).

Heavy metals (as Pb). Not more than 3 parts per million (0.003%).

Lead. Not more than 10 parts per million (0.001%).

Soluble ionizable salts (as Na_2SO_4). Not more than 5%.

Tests

Assay. Transfer about 2 grams, accurately weighted, into a tared platinum crucible, ignite at 600° for 2 hours, cool in a desiccator, and weigh. Moisten the residue with 7 or 8 drops of alcohol, add 3 drops of sulfuric acid, and add enough hydrofluoric

acid to cover the wetted sample. Evaporate to dryness on a hot plate, using medium heat (95-105°), then add 5 ml. of hydrofluoric acid, swirl the dish carefully to wash down the sides, and again evaporate to dryness. Ignite the dried residue to a red heat over a Meker burner, cool in a desiccator, and weigh. The difference between the total weight loss and the weight loss after ignition at 600° represents the weight of SiO_2 in the sample taken.

Loss on drying, page 931. Dry hydrated silica at 105° for 2 hours.

Loss on ignition. Transfer about 5 grams, accurately weighed, into a suitable tared crucible, and ignite at 600° to constant weight.

Sample Solution for the Determination of Arsenic, Heavy Metals, and Lead. Transfer 10.0 grams of the sample into a 250-ml. beaker, add 50 ml. of 0.5 N hydrochloric acid, cover with a watch glass, and heat slowly to boiling. Boil gently for 15 minutes, cool, and let the undissolved material settle. Decant the supernatant liquid through a Whatman No. 3 filter paper, or equivalent, into a 100-ml. volumetric flask, retaining as much as possible of the insoluble material in the beaker. Wash the slurry and beaker with three 10-ml. portions of hot water, decanting each washing through the filter into the flask. Finally, wash the filter paper with 15 ml. of hot water, cool the filtrate to room temperature, dilute to volume with water, and mix.

Arsenic. A 10-ml. portion of the Sample Solution meets the requirements of the Arsenic Test, page 865.

Heavy metals. Dilute 20.0 ml. of the Sample Solution to 30.0 ml with water. A 10-ml portion of the dilution meets the requirements of the Heavy Metals Tests, page 920, using 20 mcg. of lead ion (Pb) in

the control (Solution A).

Lead. A 10-ml. portion of the Sample Solution meets the requirements of the Lead Limit Test, page 929, using 10 mcg. of lead ion (Pb) in the control.

Soluble ionizable salts. Weigh accurately 12.5 grams of the sample, and stir it with 240 ml. of water for at least 5 minutes with a high speed mixer. Transfer the mixture into a 250-ml. graduate, and wash the mixer container with water, adding the washings to the graduate to make 250 ml. Stopper the graduate, and invert it several times to mix the slurry. The conductivity of the slurry, determined with a suitable conductance bridge assembly; is not greater than that produced by a control solution containing 750 mg. of anhydrous sodium sulfate in each 250 ml.

Packaging and storage. Store in well-closed containers.

Functional use in foods. Anticaking agent; defoaming agent.

VI. Description

See Table 1.

VII. Analytical Methods

1. For the determination of silica in acid-insoluble silicates such as talc or kaolin, McClellan (336) offers a gravimetric method which yields a recovery of ca 99.6%. The procedure utilizes a strong acid for dissolving the fusion melt and dispenses with evaporation for dehydrating the silica. A sample is fused with sodium carbonate (in a platinum crucible at 950-1050°C for 15 minutes. The melt is then dissolved with HNO_3 which precipitates about 95% of the silica of

the sample. This suspension is treated with NH_4Cl, $HClO_4$ and H_2SO_4, and heated for 15 minutes after the evolution of oxides of nitrogen has ceased. The cooled mixture is then diluted with hot water, filtered, and ignited, with the precipitate being weighed as crude silica. Correction for impurities is made by volatilizing the silicon as silicon tetrafluoride.

2. King, Stacy, Holt, Yates and Pickles (257) point out that all analytical methods for silica are based on the decomposition of siliceous material to liberate silicic acid. They have thoroughly reviewed prior work in some detail (257), and have undertaken a critical investigation of the basic ferric acetate precipitation procedure used for removing phosphate from solutions prior to silica determination. They find that unless there is strict control of pH, inaccurate results may be obtained, due to incomplete phosphate removal or loss of silica with the phosphate precipitation. Also they confirmed previous work that showed both phosphate and silica couple with molybdate in weak acid, but that only the silicomolybdate complex is reduced in strong acid. This principle is the basis for their procedure for determining silica in biological material, with the phosphate left in solution. Iron, in amounts greater than those occurring in animal tissue, does not interfere. In urines with high phosphate concentrations they have devised two procedures to overcome interference by precipitation of ammonium phosphomolybdate. Phosphate may be partly or completely removed by precipitation with nitrous acid and sodium molybdate is used to couple with silica.

Their colorimetric procedure agrees well with gravimetric analy-

ses, and good recoveries (in these authors' estimation) of added silica have been obtained from tissue, blood, and urine. The method was also tested on small samples of mineral dusts; results agreed well with those obtained with gravimetric methods.

3. Further attention to the phosphate interference in analysis for silica in urine has been given by Paul (384). His procedure involves precipitating the bulk of the phosphate by calcium chloride and ammonia at pH 7, and then removing the remaining phosphate by selective extraction of the phosphomolybdate with ethyl acetate. Silica is then determined in the aqueous phase after reduction of the silicomolybdate by 1-amino-2-naphthol-4-sulphonic acid in the presence of citric acid. The author indicates the method is accurate and reproducible, and generally applicable to trace amounts of silica in high phosphate concentrations.

4. Fast-neutron activation analysis has been utilized for the determination of silicon in sputum (430). The procedure was developed to identify and separate cases of silicosis from those of pulmonary tuberculosis. Sputum is digested by trypsin, centrifuged, and heated with trichloroacetic acid to remove phosphorus. For irradiation, a neutron generator with a fast-neutron yield of 2×10^9 n per cm^2 per second is used. After an exposure of 2-3 minutes, followed by a one-minute delay, the activity is measured with a multi-channel analyzer, for 4-6 minutes. The silicon content is evaluated from the aluminium-28 activity produced by the reaction $^{28}Si(n,p)\ ^{28}Al$ with a photopeak at 1.78 MeV. Although fast-neutron activation analysis by use of neutron generators had not been applied

to biological substances at the time of this author's publication, he points out that the method seems promising for such analyses.

5. Continuous on-stream instrumention is finding increased application in control analysis, and Sheen and Serfass (451) have described its application to silica determinations. In this analysis, four specific reagents are metered to the zero and sample cells of the analyzer. First a buffer is metered to maintain pH as close as possible to 1.7. Ammonium molybdate, which forms heteropolymolybdic acids with the silica and phosphorus in solution, is also metered. The complexing agent then is metered to both cells and attacks the phosphomolybdic acid, destroying it completely. The reagent has no effect on the silicomolybdic acid. Finally a reducing agent is added, resulting in the formation of colloidal molybdenum blue. This reaction always goes to completion, and therefore the color intensity is a direct measure of the soluble silica present. For the blank cell comparison, chemical reagents are fed to a cell to complete their rections before being fed to the zero cell. Each complete cycle normally lasts 12 minutes. The range of the instrument is normally 0 to 50 ppb, and a change of 1 ppb in water may be detected accurately.

VIII. Occurrence

Hydrophile polymeric silicic acids are used as food additives, to stabilize emulsions, as antisedimentation agents for cocoa in beverage mixes, as dispersing agents, and as clarifying agents for beer (291). Talc (magnesium silicate) is used extensively in Japan as a milling agent for rice (342). According to the NAS/NRC Compre-

hensive Gras Survey Report (375) calcium silicate, silica aerogel, and aluminum sodium silicate each are used in as many as 14 different categories of food, as stabilizers and emulsifiers. Talc (hydrous magnesium silicate) is used as a filler in oral pharmaceutical preparations (542) and magnesium trisilicate as an antiacid (302 and others).

In plants, the role of silicon seems to correspond to that of calcium and phosphorus in animals (262). One family of sponges has a skeleton of almost pure silica; the ash of wheat straw may contain 40% SiO_2; and the equisetum (horse tail) has been shown to contain 80% SiO_2 (262). Another indication of the high silica content of plants is its increased occurrence in tissues of herbivorous animals as compared with that of carniverous animal tissues (262).

Silicon seems invariably to be present in animal matter; also all marine forms contain silica (262). All tissues and fluids examined contain at least traces, and in many cases amounts are within the range of those of the mineral elements recognized as being normal tissue constituents (262). King and Belt (262) conclude that the almost universal distribution of silica makes it probable that silicon is a likely contaminant, if not an essential ingredient, of all protoplasm. Their data on silica in a variety of types of tissue are given in Table 2.

Table 2

Silica Content of Normal Tissues (262)

FETAL TISSUES	SiO_2 DRY TISSUE
	mgm. per 100 grams
Whole mouse[7]	10
Blood (human)[4]	13
Brain (human)[7]	22
Heart (human)[7]	20
Kidney (human)[7]	13
Kidney (calf)[7]	8–10
Liver (human)[7]	4–6
Liver (calf)[7]	4–10
Lung (human)[7]	8–10
Lung (calf)[7]	4–10
Lung (human)[8]	34
Muscle (calf)[7]	24–37
Spleen (calf)[7]	11
ADULT TISSUES (HUMAN)	
Adrenal[1]	14–80
Appendix[1]	68
Aorta thoracic[1]	11–34
Artery iliac[1]	14–50
Bladder[1]	7–21
Bone[7, 1, 3]	12–30
Brain: dura mater[1]	11–37
Brain: cortex[1]	12–36
Brain: Cerebellum[1]	16
Brain: pons[1]	13–43
Brain: pineal[1]	70–90
Cecum[1]	20–27
Cartilage: coastal[1]	18–35
Cervix[1]	11
Diaphragm[1]	11–50
Duodenum[1]	10–80
Gall bladder[1]	31

ADULT TISSUES (HUMAN)	SiO_2 DRY TISSUE
	mgm. per 100 grams
Heart: myocardium[1]	11–29
Heart: endocardium[1]	14–28
Ileum[1]	47
Kidney[1]	11–27
Liver[7, 1]	11–17
Lung[7, 8, 9, 1] (infancy to old age)	10–200
Lung[1] (infancy to old age)	14–2000
Lymph glands[1] (peribronchial)	27–5000
Mammary gland[1]	12
Milk[6, 10]	71
Muscle: pectoral[1]	15–15
Muscle: psoas[1]	23
Nerve: peripheral[1]	11–40
Nerve: spinal cord[1]	13–87
Ovary[1]	10–21
Oesophagus[1]	8–26
Pancreas[1, 5]	14–31
Parathyroid[1]	22–23
Pituitary[1]	27–67
Placenta[8]	29
Prostate[1]	11
Rectum[1]	15–74
Skin: scalp[1]	35–270
Skin: abdomen[1]	40–130
Skin: sole of foot[1]	11–59
Spleen[1]	15–41
Stomach[1]	12–12
Teeth[2]	6
Tendon, Achilles[1]	12–16
Thymus[1]	81
Thyroid[1]	21–55
Testes[1]	8–20
Umbilical cord[1]	33
Uterus[1]	7–12

The most important constituents of geological formations are the silicates. As Belt and King have pointed out (262), whole mountain ranges are composed of them. The natural silicates found in rocks, correspond to the disilicic and trisilicic acids (condensed silicic acids mentioned in Section I). For example, wollastonite ($CaSiO_3$) is a meta silicate, willemite (Zn_2SiO_4) an ortho silicate, serpentine ($Mg_3Si_2O_7$) a disilicate, and orthoclase ($KAlSi_3O_8$) a trisilicate. In the weathering process carbon dioxide dissolved in natural waters attacks those silicates which contain metals capable of combining with carbonic acid, and colloidal silica is liberated with the metal silicate being left as residue (262). Trikurakis (493) reported on a study of the goiter incidence in the high Valle of Aosta (Spain). This was attributed to high silica content of the natural water due to runoff from the mountainous and volcanic slopes, with the condition being strongest in the lowest parts of the mountain slopes.

As noted previously, silica is found in all natural waters -- mineral water, hot springs, city water, well-water and sea water. Akiya, et al., (006) collected samples of water in Japan, Europe, North and South America, and Southeastern Asia. These samples were collected in polyethylene bottles and returned to the home laboratory for analysis. Results are shown in Table 3.

Table 3

SiO_2 and $CaCO_3$ Contents in Water of America, Europe and Southeastern Asia. (006)

Place	Country	Sorts of water	Free Si as SiO_2 (ppm)	Total Si as SiO_2 (ppm)	Hardness $CaCO_3$ (ppm)	Remark.
San Francisco	U. S. A.	Drinking water		2.28	32.07	City water
Saõ Paulo	Brazil	〃		2.89	45.82	〃
Campinas	〃	〃		18.15	51.97	〃
Frankfurt	Germany	〃		7.33	32.07	〃
Hamburg	〃	〃		3.91	227.91	〃
Paris	France	〃		4.92	265.71	〃
Basel	Switzerland	〃		1.64	100.79	〃
Teheran	Persia	〃	8.0	19.2	176.0	Well water
Karachi	Pakistan	〃	6.0	8.0	100.0	City water
Bombay	India	〃	7.8	26.1	25.2	Lodging House
〃	〃	〃	17.8	42.4	590.0	Khora-village
〃	〃	〃	19.4	29.2	250.0	〃
Culcutta	〃	Bath water	16.2	34.4	460.0	Grand Hotel
〃	〃	Drinking water	17.2	22.0	430.0	〃
〃	〃	〃	6.8	13.8	72.8	Toyo Menka Co.
New Delhi	〃	〃	3.9	80.0	172.0	City water
Rangoon	Burma	Lake water	5.9	13.8	16.3	Hlawglar Lake
Singapore	Singapore	Drinking water	6.4	9.1	28.5	City water
Jakarta	Indonesia	〃	8.6	21.8	32.6	〃
Bangkok	Thailand	〃	6.4	17.6	36.2	〃
Phnom Penc	Cambodia	〃	13.4	16.6	68.0	〃
Saigon	Vietnam	〃	8.6	16.8	12.0	〃
Manila	Philippine	〃	24.1	29.2	36.0	〃

Akiya (006) also reported that Pacific Ocean sea water contains only from 0.5 to 3 ppm of silica; in general the city water of Europe and America contains from 2 to 7 ppm.

Atmospheric dust in the vicinity of factories manufacturing silicon and its alloys has been reported to contain 30 to 66% of free silica; mean concentrations of such dust of up to 3.1 mg/m^3 have been reported by Egorova (147).

IX. Stability in Containers

A study of the influence of storage time on the adsorption properties of silica zerogels has been made by Sheinfain and Stas (452). Four different zerogels were prepared from hydrogels, each with different adsorption and structural characteristics, as determined by measuring the isotherms of methyl alcohol vapor adsorption at 20°C. The samples were stored for four years in loosely stoppered jars, and methyl alcohol vapor isotherms again measured. It was found that, regardless of original structure, the prolonged storage led to decreased adsorption over the entire range of relative pressures of the adsorbate. Specifically, the data showed that the pore volume and specific surface decreased during aging, giving an increase in structure density. The authors suggested that the changes were due to the action of atmospheric moisture.

BIOLOGICAL DATA

I. Acute Toxicity

A. Animal Studies: (see Table 4).

Table 4

Substance	Animal	Sex and Number	Route	Dosage mg/kg Body Wt	Measurement	Reference
Freshly prepared Silica Sol	Mice		i.p.	50-100	LD	209
Silica Sol, opalescent and somewhat gelled	Mice		i.p.	250	LD	209
Fresh Silica Sol (ca 3%)	Mice		i.v.	100	LD (in a few minutes)	209
Fresh Silica Sol (ca 1%)	Mice		i.v.	150	LD (in 3 minutes)	209
Silica Sol, older opalescent 1%	Mice		i.v.	50	LD (in 3 minutes)	209
Silica Sol, fresh	Mice		i.v.	100	LD (2-24 hours)	209
Soluble Silica in Saline	Mice	6	i.v.	100	LD (24 hours)	209
Fresh (1/2 hr old) SiO_2 (ca 2mM)	Mice		i.v.	180 (fractionated)	LD	194
Solution above after 80 days	Mice		i.v.	9	LD	194

Table 4 (Cont'd)

Substance	Animal	Sex and Number	Route	Dosage mg/kg Body Wt	Measurement	Reference
Synthetic amorphous Silica (av particle size 0.01 μ)	Mice		i.v.	9	LD	194
Talc	Mice		i.p.	4250	LD	056
Fresh Silica Sol (ca 3%)	Rats		i.v.	100	LD (in a few minutes)	209
Precipitated Silica, particle size 19 mμ	Rats		i.v.	35.2	LD_{50} (in a few minutes)	084
Fresh precipitated Silica, particle size 20 mμ	Rats		i.v.	41.2	LD_{50} (in ca 2 hours)	084
Precipitated Silica, particle 25 mμ	Rats		i.v.	44.4	LD_{50} (in ca 2 hours)	084
Silica Condensate 150 mμ particle size suspended in isotonic saline	Rats		i. trach.	30 & 50	LD_{80-90} (in a few hours)	397
Same solution as above	Rats		i.p.	100	LD_{20-30}	397
Fresh Silica Sol	Guinea Pigs		i.p.	120	LD	209
Silica Sol, opalescent and somewhat gelled	Guinea Pigs		i.p.	200-240	LD	209
Fresh Silica Sol (ca 3%)	Guinea Pigs		i.v.	100	LD (in a few minutes)	209

Table 4 (Cont'd)

Substance	Animal	Sex and Number	Route	Dosage mg/kg Body Wt	Measurement	Reference
Fresh Silica Sol* (ca 3%)	Rabbits		i.v.	100	LD (in a few minutes)	209
Silica, 1% in isotonic saline	Rabbits		i.v.	141	LD (3 minutes, blood clot in right side of heart)	209
Silica Sol, opalescent, 3%	Rabbits		i.v.	35	LD (2 minutes, blood clot in right side of heart)	209
Soluble silica, 1.4%	Rabbits		i.v.	75 (in 7 doses, ca 1/2 hr apart)	LD (immediately after last injection)	209
Silicic Acid, 8 batches similarly prepared, but with pH varying from 1.53 to 2.65	Cats	53	i.v. (Rate of inj. varied)	15-193	Av LD	348
Colloidal Silicic Acid	Dogs	3	i.g.	25-50 cc	LD (3 days)	476
Particulate Silica (Quartz powder in isotonic NaCl)	Dogs	1	i.v.	20	LD (6 hours)	260

* The authors concluded from the nature of variation that there was no correlation between LD and pH, or between LD and injection rate. However, within each batch the LD remained in the same general range.

B. Humans

1. A fatal case of talc aspiration has been reported by Molnar, Nathenson and Edberg (351). A 22-month-old Negro boy was found by his mother, choking, breathing heavily, and coughing, with a talcum powder can beside him, and talc in his mouth. Vinegar and milk failed to induce emesis, and the child was rushed to the hospital. Initial examination indicated moderately severe respiratory distress with perioral cyanosis. The mouth and pharynx were clear; there were bilateral coarse rhonchi in the chest, with grunting; but the heart sounds were normal. Although he was given penicillin and chloramphenicol and placed in an oxygen tent with cool mist after 7 hours his respiratory distress increased. By this time bilateral moist rales and rhonchi had developed throughout both lung fields. He was then treated with lanacide C, morphine, and meralluride, for cardiotonic effect. There was some improvement, but intractable cardiopulmonary failure gradually developed and the child died 20 hours after talc aspiration. At autopsy the oral cavity, pharynx, trachea and esophagus were free of foreign material. However, the mucous membranes of the larnyx, trachea and main bronchi were covered with viscid, transparent mucus and were slightly injected. The lungs were voluminous with pink and dark red segments. The pleural surfaces were free of any exudate or nodules. A greenish-yellow creamy material filled small bronchi on the lung surface, and all organs exhibited marked congestion. Microscopically, all sections of the lungs showed focal areas of edema and emphysema, and under polarized light the distribution of talc could clearly be seen.

They were present in minute quantities, in sizes from 2 to 50 μ in length and 1 to 10 μ in thickness. Intracytoplasmic particles of talc could be detected in the leukocytes and machrophages. The post-mortem diagnosis was acute bronchitis and bronchiolitis due to aspiration of talcum powder.

A near fatal case, of talc aspiration which followed a similar course, up to the time when dexamethasone was initiated, has been reported by Hughes and Kalmer (233). The authors also cited two other fatal cases, in addition to the death described above.

2. Fatalities due to talc embolism have only recently been recognized (542). Such cases arise following intravenous use of crushed drugs, compounded for oral therapy and containing talc, by "main liner" drug addicts. Zientara and Moore (542) describe the results of an autopsy on a 31-year-old woman who had been a heroin addict since the age of 16. She was admitted to the hospital with acute respiratory failure, and died within minutes. Gross examination indicated heavy, stiff lungs with multiple hard white nodules scattered throughout the lung parenchyma; in some areas they became confluent to form larger masses. The heart was dilated with slight hypertrophy of the right ventricle. Microscopically the lungs showed talc particles in both pulmonary arteries and in surrounding interstitial tissues, causing foreign body granulomas. The walls of the pulmonary arteries were thickened, with angiomatoid lesions, and thrombi related to talc particles were present. Similiar particles were also found in the liver, spleen and kidney. The authors did not know the exact source of

the talc emboli but suspected that it was derived from methadone tablets, injected intravenously in suspension.

3. Atlee (043) has reported a characteristic retinopathy due to talc and cornstarch emboli in 17 drug addicts. The occurrence followed repeated i.v. injections of crushed methylphenidate hydrochloride tablets taken for stimulation. Opthalmoscopic examination showed tiny glistening crystals, mostly in the small blood vessels around the macula. Two of the patients, who had pulmonary hypertension, had reduced vision assumed to be caused by retinal edema. Histological examination of tissues from one patient confirmed the presence of talc and cornstarch in the retina and choroid, as well as in the lungs and brain.

II. Short Term Studies

A. Rats

1. Diatomaceous earth, the siliceous remains of unicellular and colonial algae, is used in insect control in granaries, and the grain so treated will have a residue which could conceivably be assimilated by humans (061). Bertke (061) in an effort to determine possible tissue damage studied the effects on rats over a 90-day period. Weanling white rats, Wistar strain (av wt 50 g), 15 males and 15 females were fed diatomaceous earth mixed as a 5% water suspension in their feed. Weekly weight changes were recorded, and the animals were sacrificed at 90 days. Autopsies were performed and histologic sections were made from the stomach, small and large intestines, liver, kidney, spleen, lung,

urinary bladder, adrenal glands, mesenteric lymph nodes, and testes or ovaries. Parts of the liver, kidney, and spleen were analyzed for residual silica. Two other groups of the same size received 3% and 1% respectively in their diets, with the same experimental and examination protocol followed; and the untreated group IV rats were examined as controls. Particle-size distribution measurements of the test material showed, that 90% of the particles were <0.1 mm in diameter; 55% were <0.012 mm; the smallest was 0.00046 mm and the largest 0.64 mm.

The average weekly weight gain of the 5% group was higher after the first week than the gain of the controls; the maximum weight gain differential was reached during the sixth week. In following weeks, although test animals continued to gain more rapidly than controls, the differential became progressively smaller. Projection beyond the 90 day period indicated that weight gains of the two groups possibly would be equal by the 14th or 15th week. No accurate averages were undertaken on the lower dose groups. Complete histologic studies were made on the 5% group; six rats each from the 3% and 1% categories were studied for comparison. No differences were observed in sections of these test animals when compared with sections from the controls. Silica accumulation in liver, kidneys, and spleen was negligible.

2. In another attempt to determine the damage caused by oral ingestion of silica particles McClendon et al., (337) treated six groups of weanling rats, 10 per group, with silica in the forms and of the particle sizes shown in Table 5.

These rats were fed 90% Purina Dog Chow and 10% of one of the forms listed for 3 months. A seventh group of ten untreated rats was used as a control. After sacrifice, histological examinations were made of the stomach, small and large intestine, liver, spleen, pancreas, adrenals, mesenteric lymph nodes and lung. As in the case of diatomaceous earth treatment no lesions were found in any of the organs. No analysis was made for residual silica in the organs.

3. Kochmann and Maier studied the effects of four different silicic acid preparations (273). Groups of almost fully grown albino rats, five each, were fed diets containing bread and dried milk. The first group additionally received 15 cc of distilled or mineral water containing silicic acid. The other groups were fed the same diet with the addition of commercial silicic acid preparations, i.e. Siliquid (a colloid silicic acid solution with 0.25% SiO_2), colloid silicic acid with 1% SiO_2, or Silistren (an O-silicic acid tetra glycolester with 18 to 20% SiO_2). Each of the commercial preparations contained the same amount of silicic

Table 5.

Forms and Particle sizes of Silica Fed to Weanling Rats (337)

Name	Particle size in μ
Linde silica	.02-.05
Columbia-Southern Hi-Sil 101	.03
Dow Corning silica (unpelletized)	.01-.02
Powdered silica gel	
Sodium metasilicate	
Carborundum Co. Fibrofrax (silica fibers)	

acid as the same volume of natural mineral water. Tables 6 and 7 below indicate that the total SiO_2 for the mineral water was 50 mg, and for the commercial preparations 70 mg each. Growth values are also shown.

Table 6

Experimental Series of 57 Days' Duration (273)

	Average weight of 5 rats each	
	with 15 cc H_2O	with 15 cc Silvana hot spring water
Initial weight	151 g	141.5 g
Final weight	181 g	182 g
Increase	30 g = 20%	40.5 g = 29%
Daily increase	0.53 g	0.71
Ratio of increase	100	145
SiO_2 total		50 mg

Table 7

Experimental Series of 60 Days' Duration (273)

	Average weight of 5 animals each			
	Control Animals	Siliquid	Colloid SiO_2	Silistren
Initial weight ...	85.0	94.0	90.0	92.0
Final weight	148.4	157.8	152.8	139.3
Increase	63.4 = 74%	63.8 = 68%	62.8 = 70%	47.3 = 51%
Daily increase ...	1.06	1.06	1.05	0.79
Ratio of increase	100	92	95	69
SiO_2 total		70 mg	70 mg	70 mg

The authors point out, on the basis of these data, that the animals receiving mineral water showed an increase in growth rate over that of controls. This was not the case, however, with the groups fed the commercial preparations. Animals fed on Siliquid and colloidal silicic acid had similar growth rates to the controls, while the Silistren group showed a pronounced lag in body weight increase that the authors indicated was beyond the limits of experimental error. No theory was offered for this difference, other than that the silicic acid might be in some special combination that inhibited growth. They did postulate that the increased growth rate of the mineral water group was probably due to the natural components of the water, i.e. iron, carbon dioxide etc. Accumulation of silica will be discussed later.

4. Still another investigation of the ingestion of silica in rats was conducted by Webb, Selle, and Thienes (511). They undertook the study to test the possibility that high silica content of table salt might be the etiological factor in the high silica content of eye lens and resulting cataract, as noted in India. This correlation of lens silica content with cataracts has not been found in American cases. Four series of rats were studied: Series I - controls, Series II 0.01% SiO_2 (as Braun's Air Float, 325 mesh) in their food, Series III 0.1% SiO_2, and Series IV 1.0% SiO_2. The animals were on this regime for 10 months, and then sacrificed and the tissues prepared and analyzed for silica. Eyes of none of the rats showed any pathological change in the lens or other media for transmitting or refracting light. No detrimental

changes were observed in the animals during the course of the experiment, and growth rates for all four series were the same. Some silica accumulated in the liver, spleen and testis -- particularly in series III and IV -- but lens silica values in the three test groups corresponded, within experimental error, to that of the controls. Accumulation in the various organs is discussed in more detail in Section II of Biochemical Aspects.

5. Byers and Gage (084) investigated the toxicity of "precipitated silica" -- i.e. amorphous silica prepared by acid precipitation from an aqueous solution of sodium silica in a process similar to that used for the preparation of silica gel. This is a commercially important type, according to these authors, and they undertook their investigation to assess the possibility of a silicosis hazard from its industrial use. This may not seem particularly pertinent to the evaluation of silica compounds as food additives; nevertheless, some information regarding the action of silica from such a source in the animal body may be of value. Samples from two suppliers were studied. From supplier A came A1, of particle size 19 mμ as calculated by an air permeability method; A2 of particle size 20 mμ when freshly prepared, as shown by electron microscopy, and at a later date 60 mμ as indicated by air permeability measurement. Supplier B provided Sample B of particle size 25 mμ, again as measured by air permeability. Sample A2 particles seemed to have a greater tendency to aggregate, when tested in dust cloud chamber than did those of either A1 or B. Also there was greater difficulty encountered in preparing an

aqueous suspension of A2. The acute toxicities of these three samples by i.v. injection were reported in Table 4.

Groups of 50 M and 50 F adult Wistar albino rats were injected intratrachaelly, under light ether anesthesia, with 1 ml of a 2.5% suspension of each sample. The silica had been sterilized in hot air and dispersed in sterile isotonic saline. Higher doses than 25 mg/rat caused death within 24 hours. Twelve rats from group A2 died within 4 days, presumably from lung infection since this group was not injected with penicillin as groups Al and B had been. From each group 5 M and 5 F were sacrificed at three intervals during the 12 months of the study, and lungs, liver, kidneys, and spleen were taken for silica determinations. Similar groups were also sacrificed for histopathological examination of the lungs. A significant amount of silica was detected in the lungs after 12 months, but a rate of elimination much faster than that for quartz and other fibrogenic dusts was noted. Lesions were produced, mild fibrosis, but again the authors stress they did not resemble those from quartz. Sample A2 produced the most marked effect, with the lesions the largest and most persistent, and with a slightly greater deposition of fibers than with Al and B. The lesions with all three groups regressed during the course of the experiment, corresponding to the disappearance of silica from the lungs. The authors evaluate the lung function effect of the three dust samples as small. There was evidence of mild emphysema in a few lungs but aside from a few large abscesses and foci of bronchiectasis there was little evidence of infection.

The authors conclude that the dusts did not greatly influence the incidence or course of infections, when compared to lung function of normal controls. Numerical data and detailed discussion of accumulation and excretion are discussed in a later section.

6. Silica and several silica salts were studied by Newberne and Wilson (372). Groups of 15 M and 15 F Charles River CD strain rats (BW 80 to 100 g) were fed silicon dioxide, 0.8 g/kg/day; aluminum silicate, 1.3 g/kg/day; sodium silicate, 2.4 g, or magnesium trisilicate, 1.8 g, in a semisynthetic diet. After four weeks the animals were sacrificed. The only clinical symptoms during the feeding period were polydipsia, polyuria, and soft stools, seen intermittently in a few animals fed magnesium trisilicate or sodium silicate. All clinical chemical tests were within normal limits. No drug-related lesions occurred in any of the rats, and the only observed departure from normality was an occasional rat from each group with an isolated hyaline tubular cast. Dogs treated similarly showed gross microscopic renal lesions from sodium and magnesium silicates, to be discussed in a later section.

B. Guinea Pigs

The mineral talc is a specific substance, anhydrous magnesium silicate [$H_2Mg_3(SiO_3)_4$]. Several minerals may accompany it as it occurs in nature and some of them may be quantitatively more important than talc. Most prominent are serpentine (hydrous magnesium silicate, [$H_4Mg_3(SiO_3)_4$], dolomite (calcium magnesium carbonate) and tremolite (calcium magnesium silicate). Talcs used in industry (in cosmetics, as fillers in paper, paints, as dusting

agents, etc.) vary greatly. Also it is known that talc dust exposure results in diffuse fibrosis. Schulz and Williams (441) studied the effects on guinea pigs of seven commercial talcs, choosing their samples to represent the range of composition, with regard to the $Si:CO_2$, that was covered by 51 different talcs they had analyzed. Table 8 reports the composition of the 7 samples tested.

Table 8

Talc Samples (441)

	WT. % SOLUBLE	TALC	SERP.	CARB.	QTZ.	TREM.	OTHERS	$Si:CO_2$ RATIOS
		%	%	%	%	%	%	
1. 814-6A	41.73	6	5	86	—	—	3	15:85
2. 814-11C	35.56	12	35	45	tr	tr	8	55:45
3. 814-25G	22.94	16	26	47	tr	tr	11	53:47
4. 814-33	14.68	24	30	32	tr	8	6	68:32
5. 814-40B	7.95	32	49	9	tr	tr	10	91:9
6. 814-50	1.13	52	39	—	—	—	9	100:0
7. 814-34	12.52	3	3	8	tr	82	4	92:8

Guinea pigs (BW 250 g), in groups of 10, were injected once intraperitoneally (i.p.) with a 4-cc suspension (5 g in 100 cc physiological saline) having the equivalent of 200 mg of talc. They were sacrificed at intervals from 10 days to 15 months, and tissues from the ventral parietal surface of the peritoneum (where most of the talc seemed to have accumulated) were studied by two methods. Sections were mounted, unstained, in Canada balsam and studied petrographically to determine mineralogical changes which had taken place. Also, sections were stained with hematoxylin-eosin and special stains to study histologically the changes in connective tissue.

From the mineralogical standpoint, two facts seem to warrant emphasis, according to the authors. First, most of the dolomite, which contained no silica, disappeared in 12 to 15 months with only the coarsest particles remaining. Second, in "talcs" which contained carbonate, the serpentine was also removed, but to a lesser extent. It was also noted that after a period of about 8 to 12 months talc needles tended to align themselves parallel to the abdominal wall of the animal.

Histological study showed that the material was mostly taken up and held by the giant cells. In all cases the fibrous tissue was of minimal amount; in no instance was there evidence of a progressive proliferation of the fibrous tissue similar to that found in the usual silicotic nodule. The pattern then is one of storage of foreign material, primarily in phagocytic cells, with sufficient accompanying fibrous tissue to hold these cells in place. The authors term this "storage fibrosis".

The two talcs which contained the least carbonate, 814-50 and 814-34 (see Table 8) caused the greatest amount of fibrous tissue. Studies of talcs which have been shown to cause granuloma will be reported in a later section.

C. Dogs

Newberne and Wilson (372), whose work on rats has already been reported, also treated purebred beagles with various silica compounds. The doses of each compound administered were equivalent to 0.8 g/kg/day of SiO_2, mixed in a highly palatable diet. Table 9 shows the compounds administered, and the incidence of renal lesions

that were observed after sacrifice at four weeks.

Table 9 (372)

Renal Lesions in Dogs Fed Silicon Compounds for Four Weeks

Treatment	Dose (gm/kg/day)	Sex	Incidence of renal lesions
Control	0	M	0/6
		F	0/6
Silicon dioxide	0.8	M	0/9
		F	0/8
Aluminum silicate	1.3	M	0/6
		F	0/7
Sodium silicate	2.4	M	8/8
		F	7/8
Magnesium trisilicate	1.8	M	9/9
		F	9/9

The only significant clinical abnormalties exhibited by the animals during the treatment period were polydispsia and polyuria, seen in a few dogs fed sodium silicate and magnesium trisilicate. Soft feces, discolored by unabsorbed compounds, were seen occasionally in most of the test dogs. Body weight, food intake, and urinary and blood measurements were essentially normal in all animals. Upon autopsy, gross cortical lesions of the kidney were noted in all of the male dogs and in all but one of the female dogs that were fed sodium silicate. The lesions appeared to be focal, subcapsular hemorrhages, but on the cut surface they suggested cortical infarcts. Such lesions were seen in all dogs of both sexes that had received magnesium trisilicate, but were not observed in animals fed aluminum silicate or silicon dioxide. Histopathologic studies also revealed characteristic lesions from the sodium and magnesium compounds, but none in the animals receiving aluminum silicate or silicon dioxide. The nature of the lesion was the same

in all cases, although they varied in severity from one animal to another and from one area to another within a kidney. Selected tubules seemed to be affected and were often in juxtaposition to normal ones. Occasionally, deposits of crystalline material, characteristic of mineralization, were observed in degenerated tubular epithelium, but such changes were not common. Glomeruli did not appear to be damaged. The general impression gained by the authors was one of irritation of tubular epithelium, followed by degenerative and regenerative changes; these alterations were accompanied by inflammatory cell infiltration into the interstitium.

Finally, the authors emphasize that despite the presence of extensive renal damage, impairment of renal function was not detected by any of the chemical tests made on serum or urine. Apparently, renal reserve was adequate for normal functional demands. Perhaps longer exposure to the compounds, or examination after a longer period following the end of the treatment, would have shown impairment of renal function to be tied in with more advanced renal lesions (372).

D. Humans

The effect of [redacted] atmospheric concentrations of silicon dioxide on the health of children has been reported by Egorova (147). He studied the area around a factory manufacturing ferrosilicon of 45% and 75% concentration. The factory utilized open, electric-arc furnaces, with the furnace gases being discharged at the furnace tops; the gases consist mainly of the products of sublimation and vaporization of silicon and its compounds. Table 10 shows the dust concentrations in the atmosphere at distances from

its source, and also the free silica in the dust.

Table 10 (147)

Dust Concentrations in the Atmosphere at Different Distances from the Shop Producing Ferrosilicon Alloys

Distance from the source of atmospheric pollution, km	Number of samples	% of samples found to contain dust	Mean dust concentration found in the samples, mg/m³	% of samples in which the dust concentration exceeded the max. permissible concentration of 0.5 mg/m³
Shop grounds	23	100	4.1	
0.3	25	100	3.1	100
0.5	25	100	2.5	100
1.0	26	100	2.0	100
2.0	24	100	1.75	100
3.0	25	100	3.0	100

Concentration of Free Silica and its Percentage Contents in the Dust at Different Distances from the Shop Producing Ferrosilicon Alloys

Distance from the source of atmospheric pollution, km	Number of samples	% of samples found to contain free silica	Mean concentration of free silica in the dust, %	Concentration of free silica in the dust, %	
				mean	maximum
Shop grounds	23	100	0.72	14.0	41.6
0.3	25	100	0.54	16.0	36.0
0.5	25	88	0.30	11.2	31.5
1.0	24	83	0.37	20.0	66.0
2.0	24	87.5	0.19	11.8	32.0
3.0	25	92	0.50	14.7	45.0

To insure comparability of data, studies were made of the living and dwelling conditions of the children and the economic status of their families, as well as their location and the health patterns. The disease-incidence data for the children were based on requests for medical pediatric consultations, and the records of the medical consultation service. Comparative morbidity data showed that overall the children's morbidity was 37% higher in the investigated area near the factory than in the control area

during their first year of life, 27% higher during the their second year, 30% higher in the third year, 16% higher in the 4-7 year period, and 45% higher during the 8-15 year period. Ear, nose, and throat disorders were most common among the children residing in the test area. Data on child morbidity based on those regarding diseases are shown in Table 11.

Table 11 (147)

Morbidity in Children in the Investigated Area (incidence of diseases per 100 investigated children)

Statistical parameter	Overall morbidity	Disorders of respiratory organs	Otorhinolaryngologic disorders	Infectious diseases	Diseases of digestive organs	Other diseases
			Control area			
M±m	107.5 ± 0.63	15.35 ± 0.80	37.7 ± 1.00	45.9 ±1.10	4.29 ± 0.45	3.98 ± 0.43
			Area with polluted atmosphere			
M±m	132.2± 2.49	21.92 ± 1.40	54.6 ±1.69	51.0 ± 1.70	4.57 ± 0.70	6.41 ± 0.83
	12	4.1	8.5	2.5	0.33	2.4

Regarding general development, the children in the tested area, showed a definite lag -- 71.8% of boys and 70% of girls showed medium and above-medium physical development in the tested area as compared to 91% and 89.6% respectively in the control district.

III. Long-Term Studies

A. Rabbits

Gardner and Cummings (176) designed experiments to demonstrate the relation of particle size to the amount of reaction produced by a measured quantity of silica. Quartz was administered to two groups of rabbits, eight animals per group, as 2% suspensions

(by wt) in physiological saline i.v. in the ear vein over a period of one to four months. The total dose for each animal was 1.3 g. Group I received silica particles 1 to 3 μ in diameter; Group II particles, 6 to 12 μ; and Group III, aluminum oxide particles 1 to 3 μ in diameter. Seven of the 24 animals died of embolism during the course of treatment; two more in the group receiving the finer quartz particles died of silicosis. Aside from the one animal who died during the first injection from coccidiosis, the remaining rabbits were sacrificed two to three years after completion of treatment.

Histological examination showed that particles are segregated in different locations according to their size. The largest ones are caught in the pulmonary capillaries, those of intermediate size in the spleen and hepatic lymph node, and the finest ones in the liver. The authors indicate that the fine silica particles are the most active, producing progressive coarsely nodular cirrhosis of the liver, attended by extensive destruction of the parenchyma, and followed later by regeneration in certain areas. They indicate this cirrhosis is the result of a typical, hyaline nodular silicotic fibrosis originating in the portal connective tissues. The coarse particles, 10 to 12 μ in diameter, are much less irritating, exciting a simple foreign body reaction which progressed very little in three years. Fine aluminum oxide particles of the same size as those of the smaller silica particles merely are phagocytosed and produce no fibrosis in the stroma of any organ where they were deposited. The authors believe that

these observations indicate that the injury produced by silica is specific and chemical rather than physical in character.

B. Humans

Other than studies of silicosis as an industrial disease, long-term human studies on silica intake have been very rare. Akiya et al. (006) have offered a detailed report on the relationship between silica in drinks and foods and in human blood vessels. As indicated in Section V, Chemical Information, silica is encountered by the human from much of his food and environment. The Japanese are excellent subjects for a study of this effect, because of their unusually high silica intake from talc milled rice, a staple of their diet, as well as from their drinking water. Akiya has proposed that, in addition to the calcium and cholesterol deposits, accumulation of silica in the blood vessels may be one cause of arteriosclerosis. He prepared and studied 89 aorta slides from Japanese patients. Table 12 traces the development of arteriosclerosis, with advancement in age. The author separated the aorta into three layers of the intima, media and adventitia, and determined the silica content of each layer. He noted that the silica content of the media seemed to remain somewhat constant, but that the silica content in the adventitia increased with advance of age, and its content in the intima decreased with advancing age. At the age of about 40 to 42 the quantities in these two layers reversed. It was presumed that the silica in the adventitia might have a connection with the hypertension or the arteriosclerosis that appear after 40 years of age.

Table 12 (006)

The Age, Sex, Cause of Death and View of Aorta of Samples

No.	Autopsy No.	Age	Sex	Cause of Death	View of Aorta
1	1329	3 Mon.	M	Erythroblastosis Fetalis	N.
2	1352	11 Mon.	F	Dystrophia	N.
3	1282	9	M	Acute Myeloic Leukemia	N.
4	1393	9	M	Subarachnoidal Hemorrhage	N.
(5)	16644	15	M	Poisoning of Hypnotics	N.
(6)	16724	16	M	Bacillary Dysentery	N.
(7)	16653	16	M	Drowning	N.
(8)	16671	17	M	Poisoning of Hypnotics	N.
9	1330	20	M	Pastoperative Shock	N.
10	1323	20	M	Lung-metastasis of Osteosarcoma	N.
11	1391	20	M	Myeloic Leukemia	N.
12	1264	23	F	Rhabdomyosarcoma	N.
13	1280	24	F	Abdominal Tumor	N.
14	1366	24	M	Leukemia	N.
15	1324	25	M	Esophagus Stenosis	N.
(16)	16632	26	M	Poisoning of Cyanide	N.
17	1224	28	F	Rupture of Ectopic Pregnancy	N.
(18)	16643	28	M	Lobular Pneumonia	N.
19	1284	32	M	Sepsis	N.
20	1317	32	M	Purulent Meningitis	N.
21	1380	32	M	Hepatoma	N.
(22)	16717	34	M	Valvular Disease	N.
23	1342	35	M	Unknown	N.
24	972	35	M	Unknown	N.
25	1348	35	F	Gastric Cancer	N.
26	1370	37	F	Pulmonary Cancer	N.
27	1274	38	M	Neuroblastoma	N.
(28)	16683	38	M	Acute Heart Disease	N.
(29)	16688	38	M	Fracture of Skull	N.
(30)	16694	40	M	Unknown	A(+)
(31)	16696	40	M	Cerebral Bleeding	A(+)
(32)	16629	41	F	Poisoning of Hypnotics	N.
(33)	16624	41	F	Rupture of Tubal Pregnancy	N.
34	878	42	M	Teleangioma of Femoral Bone	N.
35	1260	42	M	Pulmonary Cancer	A(+)
36	1340	42	F	Gastric Cancer	N.
37	1332	43	F	Liposarcoma	N.
(38)	16697	43	M	Acute Cardiac Insufficiency	N.
39	1347	44	M	Aplastic Anemia	N.
40	1296	46	M	Cancer of Maxilla	N.
41	1364	46	M	Pancreatic Cancer	A(+)
42	1346	47	F	Ovarial Cancer	N.
(43)	16710	48	M	Acute Heart Disease	N.
44	1261	49	M	Aortic Aneurysm	A(++) Ca(+++)
45	1265	49	F	Ovarial Cancer	N.
46	1257	49	M	Gastric Cancer	A(++)

Table 12 (Cont) (006)

No.	Autopsy No.	Age	Sex	Cause of Death	View of Aorta
47	1258	49	M	Cerebral Bleeding	A(±)
48	1383	49	M	Gastric Cancer, Pulmonary Tuberculosis	A(+) Ca(+)
49	1168	50	F	Uterine Cancer	A(±) Ca(±)
50	1278	50	M	Gastric Cancer	N.
51	1263	51	M	Esophageal Varix	A(±)
52	1361	51	M	Auricular Fibrillation	N.
53	1267	51	F	Hepatic Cancer	A(±)
54	1266	52	M	Mesothelioma	N.
55	1262	53	M	Pulmonary Cancer	A(±) Ca(+)
56	1152	53	M	Liver Cirrhosis with Hepatoma	A(±) Ca(+)
57	1281	54	F	Arhythmia	A(±) Ca(±) U.
58	1336	54	M	Pulmonary Cancer	A(±)
59	1313	55	F	Hepatic Cancer	A(±)
60	1304	55	M	Mucoepidermoid Cancer	A(±) Ca(±) U.
(61)	16652	55	F	Acute Hemorrhagic Bronchitis	A(±) Ca(±)
62	1212	56	M	Wilson's Disease	A(±) Ca(±) U.
63	1285	56	M	Miliary Tuberculosis	N.
(64)	16686	56	M	Coronary Sclerosis	A(±) Ca(±)
65	1234	57	M	Gastric Ulcer	A(±) Ca(±) U.
66	1326	57	F	Aastric Cancer, Renal Tuberculosis	N.
67	1315	58	M	Pulmonary Tuberculosis	A(±) Ca(±) U.
68	1374	58	M	Cancer of Mandible	A(±)
69	1290	60	M	Cancer of Maxilla	A(±) Ca(±)
70	1289	60	F	Cancer of Rectum	A(±)
71	1306	62	M	Pulmonary Tuberculosis	A(±)
72	1277	62	M	Unknown	A(+)
73	1358	62	M	Cancer of Colon Transversum	A(±) Ca(±) U.
74	1308	62	F	Myocardial Infarction	A(±) Ca(±) U.
75	1269	63	M	Prostatic Carcinoma	A(±) Ca(±) U.
(76)	16658	63	M	Acute Cardiac Insufficiency	A(±) Ca(±) U.
77	1101	64	M	Pulmonary Cancer	A(±)
78	1279	64	F	Abdominal Tumor	A(±) Ca(±)
79	1379	64	M	Death after Lobotomy	A(±) Ca(±)
80	1389	65	M	Cancer of Urinary Bladder	A(±) Ca(±) U.
(81)	16685	66	F	Acute Coronary Insufficiency	A(±) Ca(±)
82	1310	67	M	Pulmonary Cancer	N.
(83)	16702	67	F	Acute Pneumonia	A(±)
84	1355	68	F	Cancer of Colon Descendens	A(+)
85	1372	69	F	Hepatic Cancer	A(±) Ca(±) U.
86	1381	69	M	Gastric Cancer	A(±) Ca(±) U.
87	1388	70	F	Paralysis of Medullaoblongata	A(±)
(88)	16700	74	M	Drowning	A(±) Ca(±) U.
(89)	16703	74	F	Lobular Pneumonia	A(±)

Aortae supplied by Tokyo Medical Examiners Office are indicated No. in ( ). Others were supplied by Department of Pathology, Tokyo Medical and Dental University.

View of Aorta N.....Normal, A.....Atherosclerosis, Ca.....Calcification, U.....Ulcer (+).....slight degree, (±).....middle degree, (±).....high degree.

In general the authors also found that the human organs in the cases of arteriosclerosis contained larger amounts of silica than in other cases. Other results from this study are discussed in later sections of this monograph.

Silicosis as an industrial disease has long been recognized; in view of the great bulk of literature on the subject, and the general knowledge concerning it there seems no need to consider that condition, when it results from industrial exposure, in this monograph. When certain aspects of the disease shed light on the effects of silica from other types of exposure, there will be discussion of it.

IV. Special Studies

A. Carcinogenicity

It is well established that while cancer of the stomach in man is one of the most common of all tumors, in animals it is rare (475). Also, within the animal group, rats have been used almost exclusively for study since guinea pigs, mice, and rabbits do not develop gastric tumors. The lesions in the rat forestomach and glandular stomach usually have been described as papilloma presumably because the relatively short lifespan of the animals does not give sufficient time for malignant development.

The work of Sugiura (475), when considered in the above context, offers confirmation of the possible carcinogenic stimulation of a silicon mixture. Young albino rats, Sherman stock, from 30 to 75 days old and weighing from 60 to 125 g were placed on a mixture of 95% polished rice and 5% kieselguhr (infusorial or diatomaceous earth). This dietary regime was maintained for their lifespan. The results of this study are summarized in Table 13, and illustrate clearly that the daily oral administration of kieselguhr has a definite stimulating effect on the production of stomach lesions.

Table 13 (475)

Summary of Incidence of Lesions Observed in the Forestomach of Rats Fed Rice Alone or Rice and Kieselguhr

Experiment No.	Diet	Number of rats used	Age of rats, days	Duration of feeding, days	Number of animals with lesions	Number of animals without lesions
1	White rice and kieselguhr	10	30	49-91	9	1
2	White rice and kieselguhr	11	75	98-116	11	0
3	White rice	27	30	54-148	13	14
4	White rice	24	75	65-156	16	8
5	Brown rice	12	30	54-75	0	12
6	Brown rice and carrot	30	75	88-200	0	30

Attention is called to the negative results of Bertke [(061) Short Term Studies section, 1] on Wistar rats fed diatomaceous earth 5% in their diet. No abnormal lessions were found in the stomach, small or large intestines after 90 days of treatment and then immediate sacrifice, possibly a result of the difference in strain.

As mentioned earlier in this monograph, the Japanese prefer talc milled rice (342), and this fact has been tied to the very high incidence of stomach cancer in Japanese men. Merliss (342) quotes from work by Hirohata and Kuratsume (Brit. J. Cancer 23, 465, 1969) a rate of 67.96% per 100,000 in the male population of Japan, 7 times that of the rate for men in the United States, and the highest of the 24 nations studied.

There are numerous reports in the literature of granulomas, at times fatal, from talc used in surgical procedures (as surgical glove powder). Ross and Lubitz (421) have published a review of its incidence up to 1949. For the purposes of the monograph, a single case of talc granulomata attributed to earlier surgery should suffice to illustrate the point. Diffenbaugh (139) has reported the case of a 59-year-old woman admitted to the hospital with a history of nausea, vomiting and a weight loss of 60 lbs in one and a half years. She had a history of a pelvic laparotomy eleven years earlier at which time adhesions from about the gall-bladder were freed. Exploratory laparotomy at the time of the second admittance revealed numerous small and large grey nodular masses covering the entire peritoneal surfaces and omentum, with dense diffuse adhesions throughout the abdomen. There was no ascitic

fluid present and the stomach was normal. The nodules were removed, and her post-operative course was uncomplicated, with no recurrence of nausea or vomiting and with a pattern of weight gain. Histological examination of sections of the nodules showed a large amount of fibrillar scar tissue, with many large and small vacuoles at the margins of which were foreign body giant cells. Scattered in the dense fibrous portions were other small clusters of foreign body giant cells and large mononuclear phagocytes. Some of the giant cells had fragments of refractile material which, examined under the micropolariscope, showed a needle-like structure with double refractive properties. Another significant aspect was a mass of concentrically arranged hyalinized fibrous tissue with small crevices in the center.

The diagnosis was that of extensive foreign body granuloma, and the author postulated that physio-chemical changes in the tissues cause increase in soluble fractions of the talc which stimulates the tissues to reaction. He pointed out that similar delay of pathological changes in silicosis of the lungs is attributed to slow leaching of the silica.

A case of metastatic carcinoid tumor associated with complicated silicosis has been reported by Halonen et al. (213). The patient was a 53-year-old widow who had worked in a china factory for some six years, starting at age 28. At age 31 she had lost weight, suffered from fatigue etc., and a diagnosis of goiter was made (a condition also attributed to silica intake (493)). She was operated on at that time and the symptoms disappeared. At age

48, she suffered from acute tonsillitis and at 49 a routine chest X-ray revealed a shadow in the right upper lobe. Edema of the legs, flushing and then painful nodules of the legs developed shortly before her admission to the hospital at age 52. X-ray examinations at this time indicated tumor-like shadows in both lungs and a tumor projecting into the lumen of the cecum. A laparatomy was undertaken, and a hard tumor discovered. It was judged inoperable because when it was manipulated a severe bronchoconstriction and convulsive contractions of the small bowel suddenly occurred. The blood pressure fell to shock level, but was restored by the administration of adrenaline chloride. Samples were taken from the metastases for microscopic study; and these subsequently showed the features of a carcinoid tumor. She recovered sufficiently to return home, but returned in 5 months and died two months later. The primary tumor proved to be at the end of the ileum with metastatic nodules in the liver, spleen, mesentery, omentum, both ovaries and in the Douglas pouch. The lungs were fibrotic throughout and contained coal pigment, with double refracting particles seen under polarized light. The authors point out that the development of silicosis usually takes exposure to silica dust for at least 10 to 15 years. It is known that silicosis may progress after exposure ends, with infection usually held responsible. Many of those cases are considered to be tuberculous. In summary, while the patient's exposure to silica dust had been of only six years duration, and it ended some 15 years before the tumor-like shadow appeared in her lung, the autopsy

showed she was suffering not only from a metastatic carcinoid tumor but from complicated silicosis which had considerably progressed several years after exposure to silica had ended. The authors suggest the possibility of the action of 5-hydroxytryptamine on the development of the silicosis.

As already indicated, surgical glove talc granulomas in various intestinal and pelvic organs have been reported. Localized silica granulomas due to glove talc also have been observed in surgical scars and as a result of impregnation of the skin by siliceous particles such as glass or sand (496). However, the report of extensive granulomas of the skin seem to be somewhat unusual, and Tye (496) described the case of a 45-year old woman, admitted to the hospital because of the development of increasing numbers of lumps on her shoulders, buttocks and thighs. The nodules had been developing for about two years and were at sites where she had had as many as 500 boils over a span of 8 to 10 years. The boils had been treated by incision and drainage, and it was observed that the nodules did not appear on areas where there had been no furuncles. It had been her practice for several years to take one or two baths daily, followed by liberal dusting of her entire body with powdered talc. Hundreds of hard, slightly raised, flesh-colored nodules varying in size from 2 mm to 2 cm were scattered over her back, buttocks and anterior and posterior aspects of her thighs. Histologically, the lesions were composed of islands of granulomas with numerous foreign body cells. From electron microscope and x-ray diffraction studies it was concluded that the

foreign bodies in the phagocytic cells were talc. It was postulated that the talcum powder gained entrance through the skin at the sites of the draining or incised boils.

B. Teratogenic Effects

Ludox®, a suspension of colloidal silica from the Du Pont Co. which contains 15% SiO_2, 1% Na_2O, 0.001% NaCl and 0.003% Na_2SO_4, has been tested for teratogenic effects in the amniotic cavity of chick embryos (526). The silica particles were dense, nonporous spheres approximately 7 mμ in diameter. They remained discrete and maintained particle size on dilution in water or saline. The pH was 8.5 with minimum stability range at pH 5-6. Fertile eggs from White Leghorn flocks or from Meatline hens mated to New Hampshire roosters were incubated at 37.5°C, and the Ludox solution was injected into the amniotic cavity of eggs incubated for five days. Each egg received 0.05 mg of the diluent containing calculated amounts ranging from 0.001 to 0.25 mg. Controls, with the same incubation setting and period, were treated with saline or distilled water with the pH adjusted to that of the test material. The embryos were observed through the shell openings and dead embryos removed for gross examination. Surviving embryos were sacrificed after 15 days, and incidence and description of defects were tabulated for all embryos surviving to the 8th day of incubation. Table 14 indicates the survival and percent of abnormalities resulting from the Ludox inoculation.

Table 14

Survival and Incidence of Abnormal Development in Chick Embryos Inoculated with Colloidal Silica into the Amniotic Cavity at 5 Days Incubation (526)

mg contained in 0.05 ml diluent per egg	Total eggs	Embryos surviving to incubation day: 8	15	Total abnormal of those surviving 8 days or more. No.	(%)
Carbon 0.1	73	38	10	19	(50)
" 0.01	52	30	13	5	(17)
" 0.001	51	29	9	1	(3)
Control	72	51	27	0	

The defects included retarded lid development or exopthalmia, encephalocele or exencephaly, external edematous blebs, ectopic viscera, retarded feathering and crossed or short upper beak. Also, there were severe axial distortions and correlated limb distortions that the authors emphasize were similar to those that have been observed with non-toxic colloidal alumina.

C. Effects on Action of Bacilli

The relationship of silicosis and tuberculosis has been considered by a number of authors, as already mentioned. Detailed discussion of their findings seems outside the scope of this monograph. However, in view of the fact that silica can enter the body from the environment either through the lungs or the digestive tract in normal daily living, and circulates via the blood stream into tissues as well as being excreted via urine and feces, this relationship could be a factor in the overall picture of toxicity. For that reason the studies of Cummins and Weatherall (120) are mentioned. They have reported that in vitro studies with tubercle bacillus in both saline and silica sol cultures indicated that the growth of tubercle bacilli in blood in vitro is neither favored nor

inhibited by the presence of colloidal silica. This conclusion seemed to be in some disagreement with the earlier work of Gye and Kettle [Brit. J. Exp. Path. 3:244 (1922)] who reported that tubercle bacilli injected into the circulation of rabbits and mice tended to settle in localized subcutaneous lesions produced by various agents which brought about increased vascularity and tissue necrosis. The latter authors further concluded that the destructive action of silica on cells, whereby the foci of necrosis was produced in which tubercle bacilli could multiply, was actually a case of cell poison by a soluble derivative of silica.

In regard to other bacilli, Cummins and Weatherall (119) studied the role of colloidal silica in bactericidal action against typhoid bacilli. They concluded from their studies that colloidal silica solution preserves typhoid bacilli from lysis in human blood or serum, and that this property extends to other serum-soluble bacteria. In their experiments they found colloidal silica was able to preserve Type I pneumococci from lysis in ox bile. Also, they reported that the addition of colloidal silica solution to a cellular exudate, produced by the intraperitoneal injection of dust particles, leads to agglutination of the leucocytes and dustcells and to the preservation of a large proportion of these cells, intact though probably dead, for a period of two months or more. Finally, they concluded that it is probable that these anti-lytic and agglutinating properties of colloidal silica solution may, through interference with cytolysis, be factors in the production of the lymphatic obstruction associated with pulmonary silicosis in man.

BIOCHEMICAL ASPECTS

I. Breakdown

No information on spontaneous changes in the silica compounds or mixtures in food storage or processing was available from the survey made for material for this monograph. Regarding changes in the tissues of living animals, reference is made to the work of Schulz and Williams (441) discussed in the Biological Data section, Short Term studies. These authors reported the petrographic changes which took place in seven different commercial talcs injected peritoneally in guinea pigs. They observed that the amount of talc itself (magnesium silicate) was not disturbed in the 15-month span of the study, but that the other substances in the commerical samples, notably dolomite and also serpentine when in the presence of carbonate, were slowly leached out of the particles as they remained in the animal tissue.

II. Absorption and Distribution

A. Rats

1. Kochmann and Maier, utilizing the rats followed for growth on the four different forms of colloidal silica [(273) discussed in the section on Short Term studies] studied the whole body retention of silicic acid. Four or five animals of each series were sacrificed, ground in a meat grinder, the fresh substance weighed, dried over a water bath, and rubbed to a fine powder. The water content was determined, as well as that of fat, and nitrogen, with the silicic acid being determined by the method of Schulz [Pflugers Arch. f. d. ges. Phys. 144: 350 (1912)]. The results of these analyses are shown in Table 15.

Study on Whole Body Retention of Silicic Acid in Rats

1 Fütterungsart der Ratten	8 Naß-substanz g	9 Trocken-substanz in 100 g Naß-substanz	10 Fett in 100 g Naß-substanz	11 Wasser in 100 g Naß-substanz	13 In 100 g reiner Trockensubstanz sind enthalten: Asche 12 I. %	Asche II. %	Asche Mittelwert 14 %	N_2 %	N_2 Mittelwert 15 %	Eiweiß Mittelwert 16 %	SiO_2 I. II. %	SiO_2 Mittelwert 17 %	In 100 g Asche SiO_2 18 Mgr %	
2 Silvana, 5 Ratten	850,00	23,40	4,20	72,20	15,52	15,65	15,58	I. 14,95 II. 15,65	15,30	95,63	I. 0,015 II. 0,012	0,014	84	A
3 Kontrolle zu Silvana, 4 Ratten	705,00	21,20	6,60	72,05	17,76	17,89	17,83	I. 13,12 II. 13,12	13,12	82,00	I. 0,0123 II. 0,0167	0,0145	79	
4 Silistren, 4 Ratten	498,00	20,98	9,61	69,40	16,68	16,79	16,74	I. 15,01 II. 15,01	15,01	93,81	I. 0,0379 II. 0,0431	0,041	259	B
5 Siliquid, 5 Ratten	694,00	22,53	9,54	67,94	14,11	15,65	14,88	I. 13,74 II. 13,74	13,74	85,87	I. 0,0204 II. 0,0199	0,0201	196	
6 Kolloidale Kieselsäure, 5 Ratten	676,00	21,04	8,91	70,04	15,49	16,54	16,01	I. 14,66 II. 14,66	14,66	91,63	I. 0,0293 II. 0,0273	0,0286	179	
7 Kontrolle zu Silistren, Siliquid u. kolloidal. Kieselsäure, 5 Ratten	671,00	20,23	8,58	71,78	16,78	16,03	16,41	I. 14,78 II. 15,10	14,94	93,37	I. 0,027 II. 0,023	0,025	144	

1. Type of feeding which rats received
2. Five rats received water from Silvana mineral springs [redacted]
3. Four rats received water from Silvana mineral springs-Control
4. Four rats received Silistren (trade name)
5. Five rats received Siliquid (trade name)
6. Five rats received colloidal silicic acid
7. Five rats received Silistren, Siliquid, and colloidal silicic acid-Control of
8. Wet substance
9. Dry substance in 100 g wet substance
10. Fat in 100 g wet substance
11. Water in 100 g wet substance
12. Ash
13. Contained in 100 g dry substnace
14. Average wt. of ash
15. Average wt. N_2
16. Average wt. protein
17. Average wt. SiO_2
18. In 100 g SiO_2 ash

The authors pointed out that there was no appreciable difference between individual animals in their water content; that the fat content of older animals (series 1) was lower than of the younger ones (series 2); and that there were no characteristic differences between the groups of animals in fat-free substances, nitrogen content, or generally, ash content. They did emphasize however, that the silicic acid content of the dry substance and the ash content was lower in the heavier older animals than in the younger lighter ones, a finding which agrees with that of Schulz (originator of the analytical method for silicic acid) who always found larger quantities of SiO_2 in the organs of younger subjects. There was no apparent retention of SiO_2 in the animals fed this in the form of natural mineral water, but those fed with Silistren, and possibly those fed with colloidal silicic acid, showed SiO_2 accumulation. They were puzzled as to why Siliquid-fed animals apparently retained none. Finally, they stressed as worthy of note that such small quantities of SiO_2, the regime of their experiments, could result in any accumulation.

2. Webb, Selle and Tienes (511) in their study of rats fed SiO_2 as Braun's Air Float, 325 mesh, in their food, found some silica accumulation in liver, spleen and testis. The procedure of King and Stantial [Biochem. J. 27: 990 (1933)], with modification of pH control to insure complete removal of phosphate, was used; the results are shown in Table 16.

Table 16 (511)

Silica Content of Tissues

ORGAN	SERIES I	SERIES II	SERIES III	SERIES IV
Liver	19.0*	22.7	25.0	40.5
Spleen	10.4	16.8	42.5	59.5
Testis	17.7	18.1	51.8	47.3
Kidney	22.7	16.3	25.0	22.3
Lung	34.1	22.2	37.0	25.9
Eye	64.2	49.6	58.8	57.1
Blood	14.1	17.8	13.3	15.1
Average	19.8	20.6	32.4	35.1

* Mgm. SiO_2 per 100 gm. of fresh tissue.

These authors interpreted their results on human tissues as being in general accord with the results obtained by others, as summarized in the review article of Belt and King (262). Also, they point out that since silica is generally assumed to circulate in the blood in colloidal form it is not surprising that it is picked up predominantly by organs containing a large amount of reticulo-endothelium tissue. In regard to the eye, they note that while it contains the highest concentration of silica of any organ investigated, this seems to be a normal constituent, with added silica not accumulating there. By a series of calculations Webb et al. (511) proposed the fraction of the ingested silica that is absorbed through the gastro-intestinal tract and accumulated in the tissues. When silica was added to the food to the extent of 0.1% the quantity accumulated by the tissues represented 0.8% of the amount ingested. In series III, silica analyses were made on urine and feces for one week, and on the basis of these results, the authors propose that, of the added ingested silica, 95% was excreted in the feces, 4% in the urine, and 1%

accumulated in the tissues.

3. The lung as a portal of entry into the circulatory system has been illustrated by the study of Byers and Gage (084). Experimental details have already been given in the Short Term Studies section, 5 . The three samples tested, A1, particle size 19 mμ, A2 particle size 20 mμ and Sample B particle size 25 mμ were administered intratracheally and the rats sacrificed at intervals up to 1 year. Silica was determined in various organs by modification of the method of King, Stacy, Holt, Yates and Pickles (257) described in the Analytical Methods section of this monograph. Accumulation data is reported in Table 17 below:

Table 17 (257)

Retention of Silica by Rat Tissues

Sample	Weeks After Injection	Lungs	Liver	Kidneys	Spleen
A1	12	1,570	177	33	0
	24	755	20	12·4	1·4
	52	210	61	9·7	0
A2	12	5,150	249	138	0
	36	1,550	153	44	19
	52	720	153	56	0
B	12	652	234	34	5·8
	24	324	43	8·9	1·4
	52	108	38	12	0
Average silica content of normal rat tissue		28	37	11	5

All rats received an intratracheal dose of 25 mg. precipitated silica. Figures represent μg. SiO_2 per rat.

As can be seen from the data, silica disappeared progressively from the lungs, although it was still found in significant amounts after 12 months. Some initially appeared in the liver and kidneys of animals in all three groups, but only in A2 was silica noted in these organs after 6 months. The authors say they find no evidence

to indicate the route by which silica is eliminated from the lungs, and whether it is transported in the body as particles or in solution. It would seem appropriate, however, to call attention to the fact that A2, with its greater tendency to aggregate [as discussed in Short Term Studies Section A5] had the most marked effect on lesion formation, and the proportion retained by lungs, liver and kidneys was the greatest for the three samples.

B. Rabbits

1. Intravenous administration of silica has been studied by Mosinger, Jouglard-Duplay, Versino and Granier (359). Crystalline silica was graded by sedimentation in water, dried, sterilized, and checked under the microscope. The authors indicate the particle size to be in the range from 1 to 5 μ, with ca 80% 3 μ particles. It was suspended in "physiological solution" and injected i.v. into the marginal ear vein of tawny Bourgogne strain rabbits. The quantity administered per injection was 100 mg, with the total dose being 500 to 600 mg spaced over a period of 10 to 15 months. The animals were 3 months old at treatment initiation, and weighed 1,200 to 1,500 g (with a normal weight development noted during the experimental period). Silica in the blood was measured by a modification of the procedure of King [Bull. Soc. Chem. Biol. 12:903-909, 1939 and Biochem. J., 56:11-16, (1954)]. Normal values for untreated rabbits were measured, varying from 0.305 to 0.770 mg/100 ml blood. This averages 0.454 mg/100 ml as contrasted with the high normal of 0.400 for man [Revue Lyonnaise de Medecine, 8:1375, (1959)]. This difference the authors attribute to the

exclusively vegetable diet of rabbits. In the treated rabbits, 9 of 13 showed silica of 1 g/100 ml in the blood; when silica content was plotted as a function of time elapsed since the last injection, a decreasing curve was obtained which showed that beyond a period of two months after the last treatment the silica content of the blood reverted to normal in a majority of the cases. These authors then conclude that it is reasonable to suppose that the silica injected i.v. is localized in the receptor organs. Autopsies of the rabbits, were made and the procedure of Isaacs [Bull. Soc. Chim. Biol. 6: 157-168 (1924)] used to determine silica in specific organs. For the liver, a range of 8.8 mg to 435 mg/100 g dry tissue was found, and for the lungs 2.6 mg to 278 mg; these values emphasize the mechanical stoppage of the silica particles in the pulmonary capillaries and also the process of liver detoxication. The spleen was also heavily loaded, with values up to 200 mg. Smaller quantities were found in the kidneys, with a maximum accumulation of 37.7 mg in the parenchyma. Protein disturbances and hormonal changes, as well as lesions of the spleen, lymph nodes, lungs and aorta were noted and are discussed in a later section.

C. Humans

1. King, Stantial and Dolan (259) have reported on the silica content of tissues from humans from various age groups, and also from individuals with a variety of health conditions. Fetal tissues have shown the following silica values [as determined by the procedure of King and Stantial, Biochem. J. 27: 990 (1933)].

Table 18 (259)

Silica Content of Fetal Tissues

	Tissue	$MgSiO_2$/100 g dry tissue
Human:	lung	9.8, 8.4
	liver	3.8, 5.6
	kidney	13.3
	spleen	20.3
	heart	20.4
	brain	22.0

The normal paths of entry for silica into the body are through the lungs and the digestive tract; the greater portion of that entering by the latter route is eliminated in the feces. Some enters into the bloodstream; given the state of knowledge at that date, these authors believe this fraction was excreted in the urine without much retention by any organs of the body. However, a number of other workers have shown specific data on retention which, at times, is considerable (084,511,273 and others). As with the reports on the analysis of any substance, particularly in biological material, the analytical method is a critical factor; Table 19 (359) illustrates this statement. [redacted] Normal values for silica in rabbit blood by four different methods are shown in Table 19.

Table 19 (359)

Determination in the Rabbit
(in mg silica per kg or liter of tissue or fresh blood)

	Ramel	Isaacs	King	King et al. Stantial
Brain	0	8.8 to 18	—	—
Blood	12	—	—	3.4 to 5.8
Liver	35	0 to 5.6	150-212	96-57
Kidney	28	5-17.5	115-157	67-76
Lungs	270	3.9-12	125-139	85

Also, particularly in the case of entry through the lungs, the form of the silica, (the nature of its chemical compound, particle size etc.) are factors which can cause apparent discrepancies. This point is discussed later.

In spite of the uncertainty described above, it is of value to report the silica content of human and other animal tissues, as published by King, Stantial, and Dolan (259). Table 20 gives this information

Table 20

Silica Content of Tissues (259)

Tissue	mg. SiO_2 per 100 g. dry tissue
Human:	
Lung* (normal adult)	140
(pneumonia)	93
(silicotic)	3640
,,	1700
,,	880
,,	1630
,,	810
Liver* (stone grinder)	196
Spleen*	
(normal)	15·1
(septicaemia ♂ 30)	16·0
(bronchopneumonia ♀ 75)	43·0
(rheumatic heart ♀ 46)	14·2
(bronchopneumonia ♀ 36)	23·0
(pulmonary embolism ♀ 67)	30·0
(carcinoma ♂ 25)	45
(silicosis, fibrosis of spleen ♂)	345
(silicosis, stone grinder)	436
Mesenteric lymph gland*	
(stone grinder)	1080
Bone-marrow	26·0
(lumbar vertebra)	25·2
Ox:	
Lung	103, 109
	104, 120
	87·2, 81·2
Liver	21·6, 18·0
	12·0, 15·0
Dog:	
Lung	115
	270
Kidneys	28·7
	31·8

Tissue	No.	mg. SiO_2 per 100 g. dry tissue
Rabbit:		
Lung	430	148, 161
	369	235, 229
(young)	378	18·4, 14·2
(animal exposed to SiO_2 dust)	651	6755, 7115
,,	693	895, 785
,,	687	1002
Liver	687	12·4
	648	30·6
	378	21·4
	651	20·8, 14·3
	360	20·0
Kidney	373	16·4
	380	22·2, 17·8
	647	14·4
(animal exposed to SiO_2 dust)	651	50·0, 47·6
Lymph glands		80
Spleen	657	16·0
(animals exposed to SiO_2 dust)	360	22·5
,,	369	76·0
Hair (grey)		16·5
(white)		15·6
Guinea-pig:		
Lungs		78·0
		48·0
Hair		19·4
		20·7
Chicken feathers		15·1
		12·9

* These analyses were performed on petrol- and ether-extracted tissues obtained from the wax blocks in which they had been imbedded after fixation for microscopic section and do not represent the silica content of the tissue as a whole. We are indebted to the Department of Pathology for this material.

2. King and Belt (256) have further studied the accumulation of silica in the lungs of 35 persons employed in dusty occupations and in the peribronchial lymph glands of 132 cases of individuals having no history of exposure to industrial dust. In some cases the concentration of silica was as high in lungs with no silicotic nodulation as in those with silicotic lesions. They found no evidence of a direct association between concentration of silica and the degree of fibrosis; they also indicate that the heavy deposits of siliceous particles found in the glands of old people have not produced significant silicotic lesions.

3. An extreme case of magnesium and aluminum silicate widely disseminated throughout a human body was that of a drug addict with a history of protracted use i.v. and s.c. of paregoric in various forms, combinations, and concentrations (obtained from proprietary drugs) (083). Paregoric, in proprietary preparations such as Donnagel and Parepectolin, when crushed and injected can cause the user to receive talc (hydrous magnesium silicate) and kaolin (aluminum silicate). The man died eight hours after entry into the hospital with a typical clinical picture of tetanus, a common occurrence in s.c. drug addicts. Upon autopsy, skin sections showed numerous foreign body granulomas, with large birefringent crystals. The lungs showed foreign body granulomata within the pulmonary arterioles. In the larger pulmonary arteries angiomatoids were present. Birefringent foreign body materials were in the walls of the development as well as within the walls of the venous channels in positions adjacent to the lumina. X-ray diffraction of the material

identified it as magnesium silicate. In the liver there was extensive periportal fibrosis, with numerous pigmented macrophages containing double refractive crystals; however, no foreign-body giant cells were seen. Foreign-body material was enclosed in the macrophages of the spleen. Also, the central nervous system disclosed extremely fine, double refractile particles in nerve bundles entering the anterior roots in the cervical region. No reaction was present in these fibers. The author indicated he did not understand the absence of foreign body giant cells in the liver, and postulated that perhaps the fine particulate size of the silicate crystals, which pass through the filter of the lungs into the peripheral circulation, favors engulfment by macrophages, while the larger crystals remaining in the lungs generate the foreign body reaction.

III. Metabolism and Excretion

At present, metabolism of the various compounds of silicon that are candidates for human intake is for the most part not a definable process. The exact fate of a mineral salt such as magnesium trisilicate has been predicted by Kas'yanenko (249). He has proposed that magnesium trisilicate becomes "jelly-like" upon entering the stomach as a result of the formation of colloidal silicic acid from the neutralization of hydrochloric acid. Page, Heffner and Frey (380) further postulated that when a silicate is acted on by an acid, part of the silica so formed is precipitated as a gel and part remains in solution as a colloid. It is then probable, they state, that as a silicate passes through the digestive tract other breakdown

products are formed such as ortho-silicic acid (H_4SiO_4) which is soluble, meta-silicic acid (H_2SiO_3) and tri-silicic acid ($H_2Si_3O_8$) which are partially soluble, and di-silicic acid ($H_2Si_2O_5$) which is practically insoluble. Numerous ideas and theories of what takes place with some of the other substances in vivo have been reported in the literature and are discussed in a later section of this monograph. Excretion in a more or less straightforward context, with reference to Si, is discussed here.

A. Rats

1. Holt, Yates and Tomlin (231) utilized ^{31}Si to follow the excretion of silicic acid in rats. They found there was rapid absorption of ^{31}Si from the peritoneal cavity, and analyses of separate tissues indicated no evidence of accumulation in any of the organs other than the kidney. They postulated that the concentration in the kidney was due to the tubular re-absorption of water and the non-absorption of silicate from the glomerular filtrate. They supported this theory with autoradiographs of the kidney slices which showed general distribution of ^{31}Si throughout the organ but with a higher concentration in the medullary portion where there were tubules only. When they used the liver concentration as representative of the concentration in other parts of the body, the time-concentration curve for the kidney after the injection of 8 ml of a solution containing 1 mg SiO_2/ml showed a sharp rise to the 3 hour value, followed by a gradual decline. The liver merely showed a steady drop in concentration down to a value comparable with that found in normal tissue. Varying amounts of silicate gave a

similar sharp rise with increasing dose, followed by a rapid fall to a value even below that for liver. From this they concluded that at low concentrations the silicate was concentrated by the kidney and rapidly excreted. When injections were given at higher concentrations, the body apparently was unable to deal with it, probably because the silicate is highly polymerized.

2. The effect of Aerosil, when injected i.p. into rats, was studied by Arnold, Sasse and Strecker (041). 1000 mg in a 1% suspension was administered, with sacrifice at various periods, and sections for histographic study were prepared of the collecting tubule, glomerulus, proximal tubule, Henle's loop, and the distal tubule. The first series of studies was made after injection of Aerosil of surface area 150 m^2/g. The experiment was repeated with Aerosil 0 x 50 (38 m^2/g) (about four times coarser than the first Aerosil) and also with silicic acid gel. Upon studying the sections of the three different series of experiments, the authors were surprised to find that in the lumina of the collecting tubules, particles of the same shape and dimensions were found in both the Aerosil groups; also, particles appeared in the collecting tubules of the silicic acid gel group which could not be differentiated from the particles from the Aerosil injections. The authors interpreted this to mean that from the surface of the Aerosil silicic acid enters into solution that polymerizes in the distal nephron sections, and they further postulated a glomular excretion of silicic acid from all three initial sources.

B. Guinea Pigs

1. Four different forms of silicates were administered to guinea pigs by Sauer, Laughland, and Davidson (433), and the urinary and fecal excretions were measured.

a. Sodium metasilicate ($Na_2SiO_3 \cdot 5H_2O$) in a single dose corresponding to 80.0 mg of SiO_2 was administered orally; also four doses of the sample, each 80.0 mg of SiO_2 were given at 48 hour intervals. Silica in urine and feces was determined by the procedure of King et al. (257 of this monograph), and the "net silica excretion" (the difference between silica ingested and the silica excreted in the urine and feces) was calculated. For the single dose, given to a group of five pigs, the urinary excretion rose to a maximum of 9.7 $\pm$ 0.86 mg 48 hours after dosing, and returned to normal levels after eight days. The net silica excretion amounted to 48.3 $\pm$ 3.58 mg SiO_2 and represented ca 60% of the administered dose. After the administration of the first of four successive 80-mg doses the urinary silica excretion reached a maximum of 10.3 mg per 48 hour period, and did not increase with subsequent doses. A leveling off trend began 48 hours after the last dose, and silica excretion approached normal after eight 48-hour periods. At that time the net silica excretion was 307.0 $\pm$ 7.85 mg or ca 96% of the total dose.

b. A 2% silica sol, prepared from a solution of sodium silicate and dilute HCl, was administered i.p. in two dosages (100 mg and 60 mg SiO_2) to three and two pigs respectively. It was found

that the 48-hour maximum urinary excretion was approximately three times that obtained in the previous tests by the oral route, i.e. 28.0 mg for the 100-mg dose group and 37.1 mg for the 60-mg group.

c. A silica sol, prepared by diluting a commercial preparation with average particle size of 250 A° (25 mμ), was given orally to two groups of five animals each: 1% (93.1 mg SiO_2) and 5% (567.0 mg SiO_2). The authors indicated that in their preliminary study the undiluted sol gelled rapidly at a pH below 9, but gelling did not occur at any pH if the sol was first diluted to a concentration of 5% or less. The urinary silica was present entirely in the "soluble" or "molybdate reactive" state indicating that the silica particles of the size present in the sol were not excreted without a prior depolymerization to the "soluble" silica form. With the group receiving the 5% silica sol containing 567.0 mg SiO_2, the net excretion was 487.2 $\pm$ 21.57 mg or ca 86% of the administered dose.

d. When 4% silica sol, prepared from the above mentioned commercial sol, was administered i.p., it again caused a large increase in urinary silica excretion over that from the oral route. When 438.8 mg were administered the first 48-hour urinary excretion period reflected the maximum of 50.8 $\pm$ 4.21 mg and returned to the normal level at the end of 20 days (10 periods). The net silica excretion for this test was 277.5 $\pm$ 20.99 mg, which represented 63% of the initial dose.

e. Precipitated silicic acid (of undetermined particle size)

was given both orally and i.p. at a level of 10 ml of suspension containing 390 mg of SiO_2. The urinary silica levels resulting from oral administration followed a similar pattern to that of the oral silica sol described in section c above. The net silica excretion was 251.2 $\pm$ 25.80 mg, representing 64% of the initial dose. The authors postulate that the relatively low recovery may have been due to silica retention in the intestinal tract. For the i.p. injection, the net silica excretion was 187.0 $\pm$ 15.16 mg, or ca 48% of the injected dose. Again, they assume the remainder was retained by the tissues. The authors point out that after i.p. administration there was no well-defined increase in silica content of the fecal ash, and stress that the question of silica excretion into the intestinal tract after i.p. injection requires further study.

In summary, the authors interpret the above results as follows: (1) urinary excretion apparently was limited by restricted absorption from the gastrointestinal tract, and not by the blood transport mechanism or kidneys; in the case of the first oral tests, (section a) the silica sol prepared from the sodium silicate (section b) given i.p. in a comparable dose caused a threefold increase in silica excretion; (2) with oral administration of silica sol and precipitated silica the particles probably underwent depolymerization prior to excretion; and (3) conditions in the peritoneal cavity probably favor the depolymerization and subsequent excretion of silica. However, the reason for the greater silica urinary excretion after i.p. dosage is not known.

Finally, the authors proposed that the absorption and urinary excretion of the ingested silica is limited by its solubility in the contents of the gastrointestinal tract. They supported this view by tests which showed that when guinea pigs were dosed with 0.96 ml of tetraethyl orthosilicate dissolved in 2.0 ml of ethanol, urinary excretion values in excess of 40 mg/48 hours were obtained.

2. Settle and Sauer (445), continuing the work described in the preceding section, pointed out that when the results of the earlier experiments were considered it was noted that soluble silica in the urine did not polymerize unless the concentration exceeded 18 mg/100 ml. This indicated that the nucleus of a siliceous calculus is probably formed at some point in the urinary tract. To explore this possibility further, they treated adult guinea pigs with either 15 ml of a solution of sodium metasilicate (20 mg of SiO_2/ml and with a pH 5 adjusted with 3N HCl just prior to dosing) i.p., or orally with 2 ml of tetraethyl orthosilicate in ethanol which contained 253.8 mg of SiO_2/ml. The guinea pigs were sacrificed 24 hours after dosage, and kidney sections were prepared for histological study. Deposits found in the kidney tubules were confirmed as siliceous by ashing and by viewing by reflected dark-field illumination -- first, before and after treatment with 50% HCl, and then with 0.5% hydrofluoric acid. Such deposits were found in sections from both the i.p. and the orally treated groups. The authors point out that although the amount of soluble silica given was considerably greater than animals would normally ingest on a forage diet, the results do indicate that insoluble deposits may be formed in the kidneys if large enough quantities are given.

C. Rabbits

It is appropriate at this point to mention the work of Collet and Moussard in regard to biliary elimination of silica (103). By anesthetizing the rabbit and catheterizing the common bile duct, the bile was collected and biliary output recorded on a rheograph. Control bile was collected for 30 minutes and then the animal was injected with 1.25 cc/kg of a suspension of highly dispersed silica in distilled water into the saphenous vein. (The sample was assumed to contain a mixture of silicic acid monomers and polymers). The silica content of the samples was determined by a modified version of the method of King (check original version of 103). The biliary elimination of silica in relation to the quantity injected i.v. was considered negligible by the authors, i.e. ranging from 0.35 to 1.1% during the 6 hours following injection.

D. Dogs

1. Particulate and soluble silicas, as well as silicic acid and organic silicate (Silistren), have been administered to dogs (260) and the excretion followed. Pulverized quartz was given to dogs by stomach tube, as shown in Table 21, with the excretion pattern as indicated there. Analyses were accomplished by the procedure of King and Stantial [Biochem. J. 27: 990-1001 (1933)].

Table 21 (260)

Excretion of Silica in the Urine after Administration by Stomach Tube of 5 g Powdered Quartz, Suspended in Water

Hour	SiO_2 per 100 cc. urine mg.	SiO_2 per 100 cc. blood mg.
0	2.7	0.8
4	14.3	--
7	14.7	0.7
16	4.8	--
24	3.3	0.7

Soluble silicas -- for example solutions of sodium silicate -- could not be administered in their normal alkaline solution because dogs would immediately vomit the material. However, when they were neutralized to phenolphthalein with dilute hydrochloric acid just prior to dosage by stomach tube, the dogs tolerated the dosage well. In the stomach, deposits of gelatinous silicic acid no doubt tended to form from the 5% sodium silicate solutions, when neutralized thusly, and these were then somewhat redissolved by the alkaline juices of the small intestine. The authors believe, however, that a large part of the silicate administered this way was precipitated as silicic acid before it had been in the stomach long, and, although a portion was redissolved, a large amount still remained out of solution but was absorbed and eliminated quickly in the urine. Table 22 illustrates the results of various dose levels of sodium silicate administered as described.

Table 22 (260)

Silica Content of the Urine after Administration of Silicic Acid by Stomach Tube (1) and Ingestion (2)

1

Hours	mg. SiO_2 per 100 cc. urine
Dog [illegible]: [illegible] cc. 5 % sodium silicate neutralised by hydrochloric acid	
0	1·7
1	4·1
2	23·3
3	14·9
4	22·3
5	25·3
6	23·8
25	4·8
Dog [illegible]: [illegible] cc. 5 % sodium silicate	
0	1·9
3	72·5
[illegible]	[illegible]
[illegible]	15·2
[illegible]	21·2
[illegible]	1·6

Hours	mg. SiO_2 per 100 cc. urine
Dog 390: 25 cc. 5 % sodium silicate	
0	2·0
1	17·5
3	49·3
5	56·7
6	43·5
Dog 495: 25 cc. 5 % sodium silicate	
0	0·7
2	49·2
4	22·3
6	11·9
22	4·0
29	2·8
Dog 340: 25 cc. 5 % sodium silicate	
0	—
3	55·5
5	43·2
7	45·2
9	32·2
24	12·2
72	1·4

2

Hours	mg. SiO_2 per cc. urine	cc. of urine	Total mg. SiO_2 excreted	mg. SiO_2 per 100 cc. blood
Dog 480: 100 mg. SiO_2 as silicic acid introduced into stomach.				
0	0·015			
3	0·480			0·8
5	0·367	13·5	6·47	
7	0·357	5·0	1·86	1·7
9	0·227	11·0	3·93	
13	0·112	6·0	1·36	0·8
25	0·060	6·5	0·73	
72	0·026	22·4	1·31	
		Total	15·69	
Dog 390: 250 mg. SiO_2 as silicic acid introduced into stomach.				
0	0·014			
3	0·555			0·5
5	0·367	13·0	7·21	1·0
7	0·357	17·0	5·25	
9	0·247	17·0	6·10	0·8
13	0·132	8·0	1·98	
25	0·076	5·0	0·66	
72	0·038	36·0	2·77	
		—	—	
		Total	21·97	

The authors state that analyses of the organs of several of the dogs showed no increase in silica content over controls -- a finding that contradicts those of other workers (433,511). However, as already discussed, the analytical methodology may have been a limiting factor.

Intravenous (i.v.) studies were also conducted by these authors on female dogs (260), utilizing a continuous i.v. technique, under anesthesia with the urine collected by catheter. Dosages of 100 to 200 mg of silicic acid were injected in this manner over periods of five or six hours. During the injection period the urinary output of silica rose promptly to a high value in the first hour, and to a very high value by the end of the treatment period. The blood-level was considerably raised, although not to the extent of the urinary

elevation. The authors gave data showing that only 50% of the administered dose was recovered in the urine, and they postulated that in the case of these i.v. dosages some was probably excreted in the feces with a fairly large proportion probably retained in the body. Spleen analysis of one dog confirmed a considerably higher than normal silica content.

"Silistren", a glycol ester of silicic acid, was administered to dogs as an example of organically bound silica. An amount of silistren in water solution corresponding to 400 mg of silica was injected i.v. in two dogs. In one dog, urinary silica reached almost as high a level as that obtained with silicic acid when given by stomach tube, but in the other a more moderate increase was obtained; bloody urine and anuria resulted in the latter case. Blood silica was raised and maintained at a higher level with Silistren than with any other means tried. The authors suggest that, when present as an organic compound, the silicic acid can remain at high concentrations when it is incapable of remaining there as inorganic silicate.

E. Humans

1. Page, Heffner and Frey (380) measured the urinary excretion of silica in healthy young males following the administration of magnesium trisilicate (Tabliod - a commercial antiacid tablet, which readily disintegrates in water). Five grams were given daily in five 1 gram spaced doses for four consecutive days. Twenty-four-hour urine excretion was collected for 5 days and each specimen analyzed for silica. Table 23 reports the results of these analyses.

Table 23 (380)

Experimental Study on Same Subjects as Table 21 with Daily Oral Ingestion of 5 grams of Magnesium Trisilicate (Urinary Silica (SiO_2) -- 24 Hour Totals and per 100 cc. Urine)
--SUBJECTS--

Day	Mg. Tri. Orally	S		R		M		L		B		Mean Tse.
		Total SiO_2 (Mg.)	Mg./100 cc.	Total SiO_2 (Mg.)	Mg./100 cc.	Total SiO_2 (Mg.)	Mg./100 cc.	Total SiO_2 (Mg.)	Mg./100 cc.	Total SiO_2 (Mg.)	Mg./100 cc.	
1	5 Gm.	....	...	....	...	....	...	...	...	....	...	...
2	5 Gm.	152.0	14.6	167.0	9.09	191.0	13.1	196.0	20.0	151.5	8.51	172.1
3	5 Gm.	200.0	20.0	118.0	8.60	202.0	9.09	230.0	19.0	141.0	9.01	178.8
4	5 Gm.	....	...	203.0	10.4	152.0	10.0	152.0	10.0	114.0	8.30	162.7
5	None	96.0	10.5	40.6	2.78	89.0	9.09	45.6	3.8	50.0	3.6	64.0
6	None	....	...	33.0	2.4	....	...	28.8	2.0	11.8	1.0	24.5
Total excreted from 2nd to 5th day inclusive.		448.0		528.6		637.0		653.6		459.5		545.3
Expected excretion (calculated from mean normal daily output x number of days).		*47.4		72.8		76.0		56.8		55.2		61.6
Difference =		X 400.6		455.8		561.0		596.8		404.3		483.7

Mg. Tri. = Magnesium Trisilicate. Tse. = Total SiO_2 Excreted.

As can be noted from the table each subject took a total amount of 20 grams of magnesium trisilicate, which contained ca 9.2 grams SiO_2. The increased SiO_2 excretion from the second day until three days after the end of treatment averaged 484 mg, so that ca 5.2% of the ingested silica was excreted in the urine. No deleterious effect was noted from the ingestion of the magnesium trisilicate.

2. A case of urinary calculi containing silica (302), as described by Lipworth, Bloomberg, and Reid, is one of the very few reported in the literature. A 62-year-old man, with hiatus hernia

and resultant pyrosis had taken magnesium trisilicate for years, 2 to 4 times daily. He also had coronary artery disease, with two or probably three attacks of coronary thrombosis, and had had anticoagulant therapy; he was hypercholesteremic and for some years had been on a diet low in dairy and animal fats and high in fruit and vegetables. In June 1961 the man complained of pain and a calculus was diagnosed in his left lower ureter with blockage. He passed some calculous fragments within the next few days. Again in October of that year he passed "gravel" which was found to consist almost entirely of inorganic matter. Tests for urates, oxalates and calcium were negative, but there was insufficient material for further analysis. In June of the next year, after prostatectomy, he passed a calculus presumed from his description of pain also to have come from the left ureter. It was irregularly round, facetted, ca 0.5-1 cm in diameter, and brown in color. Calcium, magnesium, oxalate, uric acid, cystine, and xanthine were not detected. A trace of phosphate and slight amount of organic matter were present, and, upon further analysis, the material was found to contain ca 50% silica. The author points out that although the pathogenesis is obscure, and only eight previous cases had been reported in the literature, there is a possibility that silica calculi may not be a rare complication.

3. Five of the eight cases of urinary calculi mentioned by Lipworth et al. (section above) were reported by Lagergren (288). The latter author discussed the survey of some 800 patients who had passed urinary calculi. The stones were analyzed by X-ray crystallography and it was found that five of the patients passed calculi

which consisted mainly of silica, present in a finely crystalline form. All five patients had been taking magnesium trisilicate in tablet form regularly, over a period of several years, as an antiacid for gastritis or ulcer. There was no evidence that any of the patients had exceeded the manufacturers' specified doses.

4. Langendorff and Lang (291) studied the effect of polymeric silicic acid on renal SiO_2 excretion in man. Aerosil^R, as described by these authors is an amorphous aerosol with particle size between 10 and 40 mμ and a surface of 175 m^2/g, having a surface free of pores and with siloxan groups and silanol groups (5-6 μMol OH-groups/m^2) thus capable of forming hydrogen bonds. One g of aerosil is capable of taking up ca 400 mg water by multi-layer adsorption without losing the quality of a dry powder. Ca 9 mg is fixed to the surface by hydrogen bonding. Also tested were a beer-clarifying agent FK 700, which is a pure hydrated silicic acid containing 86.65% SiO_2. Ten men and two women, between 22 and 28 years of age, were given Aerosil^R or FK 700, two doses of 1.25 g in 250 ml of commercial applejuice (total dose 2.5 g), on the 4th day of a 7-day period. Twenty-four-hour urine specimens were collected on days one to seven and samples from each were frozen until analyzed for SiO_2 content. The determinations were made by the method of Bauman [Z. physiol. Chemie 319: 38 (1960)], with an attempt to determine also polymeric SiO_2 (SiO_2 determination after alkaline hydrolysis). As a rule, somewhat higher values were found for "total SiO_2" but these fell within the limits of error of the method. This fact tends to support the finding of Settle and Sauer (445) that soluble silica in the urine

does not polymerize below 18 mg/100 ml. Table 24 gives the results of these analyses.

Table 24 (291)

Aerosil® Preparations

1 Tag / Vpn.-Nr. 2	1			2			3			10			11			12		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
1	0,80	26,2	33	1,78	85,1	48	0,93	64,7	67	2,01	51,6	26	1,05	14,0	13	1,39	34,6	25
2	0,77	28,1	36	1,84	119,8	65	1,07	92,0	86	1,62	23,6	15	0,76	24,6	32	0,75	32,5	43
3	0,98	49,3	50	1,20	55,7	46	1,28	31,7	25	1,13	45,9	41	0,75	37,3	50	1,08	41,2	38
4	0,73	30,0	41	1,91	75,2	39	0,81	61,9	76	1,69	83,9	49	0,89	35,7	40	1,05	39,9	38
5	0,69	50,0	72	1,50	56,0	37	2,40	101,5	42	1,65	66,1	40	1,21	49,1	41	1,63	65,3	40
6	0,63	23,6	37	1,15	47,7	41	0,97	34,6	36	0,82	35,1	43	0,67	57,5	86	0,83	41,5	50
7	0,54	25,7	48	2,27	78,9	35	0,72	47,0	65	1,57	58,1	37	1,00	35,5	36	1,14	64,8	57
1.–3.	2,55	103,6		4,82	260,6		3,28	188,4		4,76	121,1		2,56	75,9		3,22	108,5	
4.–7.	2,59	129,3		6,83	257,8		4,90	245,0		5,73	243,2		3,77	177,8		4,65	211,5	
3 Mittelwert 1.–3.	0,85	34,5	41	1,61	86,9	54	1,09	62,8	57	1,59	40,4	25	0,85	25,3	29	1,07	36,2	34
Mittelwert 4.–7.	0,65	32,3	49	1,71	64,5	37	1,23	61,3	50	1,43	60,8	42	0,94	44,5	47	1,16	52,9	45

4 Spalte 1: Harnvolumen, Liter; Spalte 2: tägliche SiO_2-Ausscheidung in mg.
Spalte 3: SiO_2-Konzentration in µg/ml.

FK 700 Preparation

1 Tag / Vpn.-Nr. 2	4			5			6			7			8			9		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
1	0,94	46,4	49	0,95	34,3	36	1,01	66,6	66	1,43	17,6	12	1,07	33,0	31	0,75	33,7	45
2	0,76	50,8	67	0,72	33,9	47	0,94	73,1	78	1,28	16,2	13	1,32	49,1	37	0,85	27,4	32
3	0,74	30,0	40	1,33	42,2	32	1,10	74,6	68	1,46	14,5	10	1,63	37,7	23	0,55	21,0	38
4	0,85	53,3	63	1,81	55,8	31	1,20	48,9	41	1,77	24,6	14	1,45	44,7	31	0,96	28,8	30
5	0,90	62,7	70	1,77	61,8	35	2,58	142,3	55	0,87	19,5	22	0,81	45,6	56	0,68	26,6	39
6	0,72	50,7	70	0,90	75,2	84	0,83	75,7	91	1,20	20,6	17	0,93	44,0	47	0,60	11,7	19
7	0,98	42,0	43	1,08	35,1	33	0,86	58,2	68	1,46	17,0	12	1,55	98,8	64	0,53	19,9	38
1.–3.	2,44	127,2		3,00	110,4		3,05	214,3		4,17	48,3		4,02	119,8		2,15	82,1	
4.–7.	3,45	208,7		5,56	227,9		5,47	325,1		5,30	81,7		4,74	233,1		2,77	87,0	
3 Mittelwert 1.–3.	0,81	42,4	52	1,00	36,8	37	1,02	71,4	70	1,39	16,1	11	1,34	39,9	30	0,72	27,4	38
Mittelwert 4.–7.	0,86	52,2	60	1,39	57,0	41	1,37	81,3	59	1,33	20,4	15	1,19	58,3	49	0,69	21,8	31

4 Spalte 1: Harnvolumen, Liter; Spalte 2: tägliche SiO_2-Ausscheidung in mg.
Spalte 3: SiO_2-Konzentration in µg/ml.

1. Day
2. Experimental subject number
3. Mean value
4. Column 1: urine volume, liter;
   Column 2: daily SiO_2 excretion in mg;
   Column 3: SiO_2 concentration in µg/ml

As can be expected, and also noted from the table, excretion varies greatly between individuals and from one day to the next in the same individual, possibly due to variations in diet or liquid intake. For the group, during the preliminary or control period, the SiO_2 concentrations were between 11 and 70 µg/ml with average daily excretion between 15.1 and 86.9 mg SiO_2. After the administration of 2.5 g Aerosil^R the SiO_2 excretion did not clearly change. In some individuals there was a reduction after one day of treatment, while the others showed an increase in SiO_2 excretion. With FK 700 (2.15 g SiO_2) there was a somewhat clearer picture. SiO_2 excretion increased in all subjects on the fourth day of treatment, with the exception of one whose SiO_2 excretion decreased 26 mg. However, the author points out that in general, in both groups, neither the increased excretion in individual cases nor the total SiO_2 excretion during the four days following the administration was related to the quantities of 2.5 or 2.15 g SiO_2 administered. No mention was made as to the possible fate of the bulk of the SiO_2 -- absorption in the tissues or excretion in feces.

Various values have been estimated for the maximum limit of silicic acid in the monomeric state, when in water or urine: Settle and Sauer (445), 18 mg/100 ml; Thomas [Dtsch. Z. Verdauungs - u Stoffwechselkrankheiten 25: 260 (1965)], 120 µg/ml (12 mg/100 ml); and Bauman [(Z. physiol. Chemie 320: 11 (1960)], 600 µg/ml (60 mg/100 ml). However, the SiO_2 concentrations found in urine in these experiments are below the range in which polymeric SiO_2 harmful to the urinary tract is formed.

5. In an effort to determine if a relationship exists between urinary silica excretion and silicosis, Whitehouse (521) administered four different types of dust as well as silicic acid, to humans by mouth. Administered in suspension with 200 cc of water about half an hour before the mid-day meal were: quartz, with particle size 6 μ; flint of the same size; scotch whinstone of the same size (described as a rock containing no free silica, silicates being present chiefly as labradorite, augite and serpentine); and precipitated silica obtained from sodium metasilicate in the usual way. A dose of 0.2 g of silicic acid (the soluble silica) was also taken by mouth. The urinary output of SiO_2 from these substances is shown in Table 25.

Table 25 (521)

The Effect of Oral Administration of Silica on the Excretion of Silica in Urine

EXPERIMENT NUMBER	DOSE TAKEN BY MOUTH	DATE	VOLUME OF URINE	SPECIFIC GRAVITY OF URINE	SiO_2 IN URINE	TOTAL SiO_2 IN 24 HRS. URINE
			cc.		mgm./100 cc.	mgm.
	—	16/ 5/35	1724	1.016	0.85	14.7
	—	17/ 5/35	1718	1.015	0.73	12.5
	—	22/ 5/35	1506	1.019	0.90	13.6
I	2 gm. whinstone	23/ 5/35	1207	1.019	1.27	16.5
		20/ 5/35	1545	1.018	0.78	12.1
II	1 gm. quartz	30/ 5/35	1387	1.019	0.62	8.6
		5/ 6/35	1783	1.014	0.61	10.9
III	3 gm. quartz	6/ 6/35	1610	1.017	0.67	10.8
		7/ 6/35	1626	1.016	0.43	7.0
		17/ 6/35	925	1.023	1.28	11.8
IV	6 gm. quartz	18/ 6/35	1596	1.016	0.74	11.8
		27/ 6/35	1850	1.014	0.70	13.0
V	0.2 gm. silica as silicic acid	28/ 6/35	1590	1.020	7.82	124.4
		3/ 7/35	1345	1.018	0.78	10.5
VI	9.3 gm. quartz	4/ 7/35	1595	1.014	1.12	17.8
	—	5/ 7/35	1270	1.019	0.83	10.5
	—	1/ 8/35	1480	1.020	0.82	12.1
VII	0.5 gm. precipitated silica	2/ 8/35	2117	1.019	0.67	14.2
		22/ 8/35	1095	1.026	1.44	15.8
VIII	2.5 gm. precipitated silica	23/ 8/35	1485	1.020	2.40	35.7
		30/ 9/35	1775	1.018	0.63	11.2
IX	6 gm. flint	1/10/35	1985	1.019	0.55	11.0
		28/10/35	1650	1.015	0.88	14.5
X	6 gm. whinstone	29/10/35	1855	1.014	2.40	44.5
		1/ 4/36	1260	1.017	0.68	8.6
XI	0.22 gm. flint*	2/ 4/36	1545	1.016	1.07	16.5
		8/ 9/36	1720	1.013	0.76	13.1
XII	2.28 gm. flint*	9/ 9/36	2040	1.014	1.38	28.1

* Maximum particle size 1 μ.

It was recognized that for positive or increased urinary SiO_2 excretion either the dosage must be increased or the range of particle size decreased, and this was undertaken. Flint dust of 1 μ was prepared by water sedimentation and administered in water as in the first series of experiments. Results from this study, along with additional data on separate samples of urine from individuals receiving precipitated silica, silicic acid, and whinstone are shown in Table 26.

Table 26 (521)

Urinary Excretion of Administered Silica

EXPERIMENT NUMBER	DOSE TAKEN BY MOUTH	SAMPLE	PERIOD OF URINE COLLECTION	VOLUME OF URINE	SPECIFIC GRAVITY OF URINE	SiO_2 IN URINE	TOTAL SiO_2
			hrs. after dose	*cc.*		*mgm./100 cc.*	*mgm.*
V	0.2 gm. silica (as silicic acid)	(a)	0–5	452	1.015	17.52	79.2
		(b)	5–12	560	1.018	5.72	32.0
		(c)	12–21	490	1.023	2.28	11.2
		(d)	21–24	88	1.024	2.28	2.0
VIII	2.5 gm. precipitated silica	(a)	0–4	246	1.030	6.03	14.8
		(b)	4–10½	313	1.028	4.74	14.8
		(c)	10½–12	114	1.023	1.68	1.9
		(d)	12–22	753	1.017	0.45	3.4
		(e)	22–24	59	1.026	1.43	0.8
X	6 gm. whinstone	(a)	0–4	350	1.020	5.42	19.0
		(b)	4–8½	1080	1.012	0.85	9.2
		(c)	8½–12	227	1.023	4.02	9.1
		(d)	12–24	198	1.029	3.63	7.2
XII	2.28 gm. flint	(a)	0–1½	680	1.011	1.04	7.1
		(b)	1½–4	250	1.015	2.77	6.9
		(c)	4–8	400	1.014	1.12	4.5
		(d)	8–12	225	1.028	2.39	5.4
		(e)	12–24	485	1.018	0.86	4.2

With the larger dose of the fine-particle-size flint, a definite increase in urinary silica excretion was noted; the same was true for precipitated silica and, to a greater extent, silicic acid. In the case of the Scotch whinstone the daily output of urinary silica was increased to at least three times the normal figure -- a result the author did not expect in view of the lack of free silica in the rock. However, on the basis of solubility studies on the substances tested, he concluded that solution of the whinstone had been caused by the action of the acid gastric juice. The author reminded readers that variations in the silica content of different water supplies should be taken into account in considering relative values, and also diet, particularly if silica is ingested in such a state that it is readily absorbed -- e.g. beer, water etc.

IV. Effects on Enzymes and Other Biochemical Parameters

A somewhat general condition, while not of extreme or necessarily permanent nature, has been shown to be adversely affected by the administration of a drug containing silica. Rohm, Seybold and Pirtkien (420) have discussed the induction of ulcers in the antestomach in rats and the influence of ten different drugs commonly used in human gastric therapy. Male Wistar albino rats were treated with a 20% glucose solution administered from drinking tubes; the treatment lasted for eight days. The various drugs were in part dissolved in the glucose, and in part injected s.c., i.m. or i.p. The rats were sacrificed and the stomach carefully removed for histological examination, with the ulcers being evaluated according

to number and size. Of the ten drugs, only one appeared to inhibit ulcer formation, and this conclusion was not statistically confirmed. Five, however -- among them aluminum sodium silicate with 0.5% belladonna extract (Belladonna-Neutralon) -- produced a statistically confirmed increase in ulceration.

A. Renal Mechanisms and Lesions

1. In an often quoted work, Policard and Collet (398) described their experiments with the injection of strong concentrations of fresh silica gel into the peritoneal cavity of albino rats. The silica gel was prepared by electrolysis of sodium silicate, which yields a very pure product with silica concentrations ca 5%. This is a polymer of silicic acid SiO 3112 with a consistency of a semi-solid gel. It was sterilized with UV rays and chemically analyzed to establish a volume to weight ratio for SiO_2. The gel was administered, i.p. 45 to 90 mg of silica, in a single dose. The animals were sacrificed or died spontaneously in from 16 hours to 20 days. Kidney sections were prepared for histological study and the following observations then made. Sixteen hours after injection a typical acute toxic epithelial nephritis was noted, recalling mercury nephritis, without glomerular involvement. At about the seventh day, a transitional period was noted during which the toxic nephritis subsided and foci of interstitial nephritis appeared. As a rule this period was marked by a large number of inflammatory lesions of the pyelonephritic type, with highly dilated tubules. After this period came a phase of progressive tubular atrophy and interstitial fibrosis and glomerular alterations which the authors term interstitial

glomerulonephritis.

2. In a later study from the same laboratory the effects of oligomeric silicic acid were considered (399). This acid was found capable of penetrating by diffusion into the mitochondria of the renal epithelium of rats that had received i.p. silica gel some hours previously. Inside the mitochondria, where a different equilibrium medium existed, the silica polymerized and became visible in the high resolution microscope in the form of very fine, very dense granulations measuring some 40 A° (4 mμ). These granulations were joined together and formed very dense heterogenous granular masses of a size varying between ca 200 and 500 A° (20-50 mμ). They were always situated between the widely spaced internal membranes of the mitochondria. After the development of these silica deposits, the mitochondria do not remain normal. Two types of conditions progress. First, the mitochondria undergo swelling, with internal membranes becoming widely separated and progressively fainter. The silica masses increase and gradually the outlines of the mitochondria blur. They appear to break up in the surrounding cytoplasmic milieu which is much altered by edema; the masses of silica are then free in the protein magma resulting from the degeneration of the renal epithlial cells. This magma occupies the lumen of the tubules and constitutes the well-known "granular casts." This swelling does not seem to be directly dependent upon the presence of the silica masses however, as the adjacent mitochondria without silica masses may reveal identical alterations. The swelling appears to be related to a condition of the ambient cytoplasmic milieu, which could possibly be the presence

of diffusible oligomeric silica in the cytoplasm. In a second type, instead of being swollen the mitochondria become denser without changing dimensions. The light and swollen mitochondria and the denser mitochondria are not mixed together, but seem to occur in adjacent zones of the degenerated epithelium. The two types of mitochondria, together with their silica masses, reappear in the casts that occupy the lumen of the injured urinary tubules. These casts then are carried by the glomerular urine and are excreted. In the urinary tubules cleared in this way, the regeneration of a new epithelium may take place. The authors compare this circuit of elimination with the purification of the lungs where the degenerated alveolar cells, progressively eliminated through the bronchial passages, rid the lungs of silica particles. In neither case, kidney or lung, is the purification process entirely complete, and this is the cause of persistent and often progressive sclerotic foci (pneumoconiosis or sclerous silicotic nephritis).

3. Markovic and Arambasic (329) induced chronic interstitial nephritis in guinea pigs by administering pure silica (quartz), of particle size 1-3 mu in diameter, in drinking water for a period of several months. The animals developed renal pathological changes similar to those found in man in Yugoslavia. Endemic nephropathy was attributed to rock erosion in village communities on the banks of the lower reaches of large rivers. According to the authors, the renal lesions observed in such a situation were caused by release of silicic acid, and specifically involved a dystrophic-atrophic lesion in the parenchyma and a proliferative-inflammatory lesion

in the interstitial tissue.) The lowest concentration of silicate suspension that induced interstitial nephritis in the animals was 50 mg/liter of water -- a quantity of SiO_2 detectable in the drinking water in areas where human endemic nephropathy was observed. Also, the authors point out that the human kidney is more sensitive to silicate than the kidney of herbivorous animals because of the acid pH of the human urine.

B. Serum Protein and Protein Biosynthesis Alterations

1. Amorphous and crystalline silicon dioxide have been studied for their effect on blood protein fractions and histamine (186). Gel'fon and Fedorova treated white rats, M, BW 250 to 300 g with 50 mg of silica gel dust suspended in 1 ml of physiologic saline, injected intratracheally. A second group was treated similarly with 50 mg/ml of crystalline silicon dioxide dust also in physiologic saline. Particle sizes were 1 to 3 μ. The animals were sacrificed 1, 2, 4, and 7 months after injection. Serum proteins were determined by paper electrophoresis. The administration of crystalline silicon dioxide resulted in a slightly elevated total protein level in the serum, decrease in albumin, and increase in the globulins (mainly β- and γ- globulin fractions). In this group histamine increased in the lung tissues. In the amorphous-silicon-dioxide treated groups, the trends were the same but less pronounced, and abnormal values occurred later than with the crystalline group. The lungs contained cellular dust foci unlike the silicotic nodules typical of experimental silicosis in white rats, focal thickening of the septa, signs of emphysema, and slight peribronchial and perivascular

sclerosis. In rabbits injected s.c. with quartz dust, the serum albumin level was lowered, and there was a gradual increase in the amount of globulins (γ-globulins in particular) and in blood histamine. Quartz dust, when administered to rats who had been previously immunized with typhoid vaccine caused greater changes in the serum albumin content and the β- and γ-globulins than when administered to nonimmunized animals. However, the morphological changes in the lungs and lymph nodes were almost identical in both groups of animals.

2. An in vitro study of silica effect on protein biosynthesis by rat-liver cell-free systems (105) has shown that leucine incorporation into microsomal protein was depressed by both crystalline HF-treated silica (tridymite) and vitreous (HF-treated) silica. As can be seen from Table 27, the effect was more pronounced with the crystalline form, a circumstance which the authors interpret as probably related to the surface structure of the silica particle.

Table 27 (105)

In Vitro Incorporation of DL-leucine-1-C^{14} into Rat Liver Microsomal Protein.
Each figure (c.p.m. per mg protein) is the mean ± S.E. of 2 flasks

Experiment	Control	Crystalline silica	Vitreous silica
1	92.5 ± 4.47	52.0 ± 1.25	..
2	80.5 ± 5.48	59.0 ± 5.00	–
3	116.0 ± 3.00	62.0 ± 1.40	–
4	111.0 ± 9.00	65.0 ± 6.00	
1	81.0 ± 3.00		65.5 ± 7.48
2	75.5 ± 10.49		13.0 ± 6.00
3	84.0 ± 10.00		76.5 ± 3.46
4	80.5 ± 5.48		62.5 ± 7.48

The statistical evaluation of data has been made with the analysis of variance test.

3. Repeated intravenous injections of 1-5 μ silica in 100 mg doses were given to rabbits (359), with the total dose of 500-600 mg spread over a 10-15 month treatment period. The proteinograms, developed by electrophoresis, revealed essentially an imbalance in the albumin-globulin ratio in favor of the globulins. There was a distinct increase in all cases in the β- and γ-globulins, a phenomenon which agrees with the observations of Gel'fon (186) on rats, Mosinger (357) on rabbits and Autio (045) on dogs. In this study (359), there was also an increase in the α-2-glycoglobulins and β-lipoproteins. Furthermore, there was a reduction in urinary 17-ketosteroids, ca 50%, in both male and female animals. Histologically, in the liver a non-specific cirrhotic process was observed with nodular silicosis. Silicotic lesions were also seen in the spleen, lymph nodes, and lungs. The pulmonary silicotic nodules invariably had a septal topography and always developed around pulmonary capillaries. They were accompanied by pulmonary emphysema. In the kidneys there was always glomerulitis and tubular nephritis. Finally, diffuse amyloidosis was observed, with diffuse calcinosis; aortic lesions; and general mesenchymal, visceral and neuro-endocrine reactive syndrome.

C. Blood Lipids

Szabo, Mody and Szekely (481) have reported on the effect of silicic acid and silica dioxide on blood lipids. Twelve rabbits were injected s.c. 5 times in a period of 11 days with 0.5 ml/kg of an 0.5% solution of colloidal silicic acid. They also received 20 mg cortisone i.m. daily. Serum proteins and lipoproteins were determined

before (for control base) and one and two weeks after the first injection. Every animal developed severe dysproteinemia. The blood lipid level rose and the relative and absolute amounts of the β-lipoproteins increased, as did the β/α ratio. Cortisone had no effect on the changes. Heparin (400 units) restored the normal blood-lipid and β-lipoprotein levels. In another series of tests, 14 dogs were injected i.v. every 2 or 3 days over a period of 30 days with 2 ml/kg of the same colloidal silicic acid solution. Again serum proteins and lipoproteins were determined before and every 10 days after injection. The amount of lipoproteins was high in all cases and the β/α ratio markedly increased. Guinea pigs, in the third test by these authors, were studied for the effect of silicon on serum cholesterol level. Twenty-six pigs were given a single i.p. injection of 50 mg of silicon dust or 10 mg of amorphous silicon dioxide. The blood cholesterol level rose significantly on the average to 118.1 $\pm$ 8.7 and 109.6 $\pm$ 9.3 mg% respectively, the control value being 84.7 $\pm$ 2.4 mg%.

D. Enzyme Changes

1. Talc has been observed to cause a decrease in hepatic catalase activity (245). Strong A mice were given s.c. injections of 1.0 ml of a 0.67% suspension of talc. A transient, but marked, rise in catalase activity was observed on the 4th day following injection. The rise in activity was manifest mainly in the mitochondrial fraction, with concomitant increased incorporation of radioactive leucine in the microsomal fraction. The authors propose a relationship between the increased catalase activity and increased incorporation of

leucine. Attention is also called to the *in vitro* study of silica effect on protein biosynthesis by the rat liver (105) discussed on page 88 of this monograph.

2. Webster *et al.* (513) have studied some of the biologically active substances produced in the state of "silica shock" in rabbits and guinea pigs. Using Aerosil [of particle size 100-400 A° (10-40 mμ)] and ground silica of particle size <1 μ, suspensions were made to contain 25 mg in 2 ml which were injected into a vein in one ear. Analysis of serum of the animals in the resulting state of shock indicated an increase of a kinin, probably bradykinin, and the authors suggest that the release of a kinin may be a factor in the cause of death in a state of silica shock.

E. Effects on Blood Cells, and Clotting

1. Zaks and Galeniyetse (537) have measured the heparin number of blood and heparinocytes after oral administration of silica gel to 11 healthy humans. They received silica gel, 2.5 ml of a 20% sodium silicate solution neutralized with normal HCl acid solution, for 21 days. After receiving the gel, the humans exhibited an increase in the heparin number, the first symptoms appearing about the 7th day. A statistically significant increase in the heparin number was observed on the 21st day. The number of basophilic leukocytes decreased on days 7 and 11 and increased on days 14 and 21, but did not reach the baseline level.

2. The effect of colloidal silica on blood clotting was reported by Margolis (327). He found that the silica accelerates blood coagulation by adsorption and partial denaturation of a specific

plasma protein, the Hageman factor. Quantitative measurements showed that the activity of the silica depends on the particle diameter, and indicates that somewhere between 10 and 2 mμ there is a critical minimum particle size below which silica ceases to activate plasma.

3. The hemolytic effects of colloidal silica (217) and aerosil, crystalline silica, silicic acid powder, and silica gel (316) have been studied. A detailed discussion of the in vitro studies on human cells (217) and sheep erythrocytes seems beyond the scope of this monograph. However, it is appropriate to point out that Margolis (217) indicates that this phenomenon, as with the effect of colloidal silica on blood clotting, may be related to the geometrical relation between the colloidal particles and the protein molecules.

V. Drug Interaction

1. The now well established phenomenon of intraperitoneal adhesions due to talc has been considered in relation to cortisone effect (056), with what the authors consider to be definitive results. A total of 89 talc-injected mice were each given s.c. 0.5 mg cortisone daily from the day of talc injection until sacrifice. Talc was administered 35 mg i.p., as 0.35 ml of a 10% suspension. In a second series, 13 additional mice were given cortisone daily only during the first 10 days, and 13 more daily only during the last 10 days. In a third series eight mice were pretreated daily with cortisone for 14 days before talc injection, and then daily for an additional seven days. Histological examination showed that although cortisone delayed the onset of formation of abdominal adhesions due to i.p.

injection of talc after the adhesions had been formed, cortisone had no effect in promoting their resolution.

2. Also, the influence of cortisone on leptomeningeal reactions induced by talc has been studied (379). Eighteen rabbits received intrathecal injections of 1.0 cc of talc suspension with sacrifice in 15 days. Ten of these animals were treated with daily injections of cortisone 5 and 10 mg/kg. The control (talc only) animals developed a meningeal reaction consisting of the appearance of histocytes, macrophages and giant cells, while the cortisone treated rabbits showed a marked diminution of the meningeal response to the talc. Preliminary experiments with the use of hydrocortisone, injected intrathecally (10 mg) on the 1st and 7th days also suggest diminution of the meningeal response to talc, though not as strikingly so as with i.m. cortisone.

3. Silicon compounds have been noted to have an effect on the formation of atheroma (platelet deposits of cholesterol), and Loeper and Loeper (305) have investigated the use of sodium silicate, lysine silicate, and the organic silicon compounds, silanol salicylate and silanol citrate. The control rabbits were kept on an atherogenic diet that included 0.75 g/day of cholesterol dissolved in oil, while other groups were kept on the same diet while receiving:
(a) sodium silicate i.v. in a dose of 0.01 g on alternate days, (b) lysine silicate p.o. 0.01 g/day, and (c) silanol salicylate (monomethyltrisilanol salicylate) i.v. 0.0075 g on alternate days or (d) silanol citrate (monoethyltrisilanol citrate) i.v. 0.02 g on alternate days. After sacrifice at two months, gross examination

of the entire aorta was made and histological examination with lipid staining was carried out. The results are shown in Table 28.

Table 28 (305)

Effect of Silicon Compounds on Experimental Atheroma

Diet	Rabbits	Atheromatous rabbits
Cholesterol	8	8
Cholesterol + sodium silicate	8	3
Cholesterol + lysine silicate	5	2
Cholesterol	8	5
Cholesterol + silanol salicylate	5	0
Cholesterol + silanol citrate	4	1

With regard to the histological examination, the authors noted that in addition to atheromatous plaques in the controls, the fine fragmented elastic fibers were frequently altered (in 15 of 22 rabbits), and there was increased metachromasia of the basic substance in the subintimal region and the media. In the treated animals, however, alteration of the elastic fibers was rare (6 of 23 animals) and, interestingly, the elastic fibers not only were intact but often were more numerous and thicker in the three aortic layers and were without collagen proliferation. This reaction was particularly marked in organic silicon compounds. Metachromasia of the basic substance was increased in both treated animals and controls. The

authors discussed the theory that the effect of silica compounds might be due to increased impermeability to lipids, but concluded that it seemed more likely it is linked to the protection and development of the elastic fibrils of the aortic wall.

4. Several other examples of the interaction of silica compounds with drugs can be found in the works of Grelet (206), Daniel-Moussard and Collet (129), and Marks (331). Grelet (206) investigated the role of vitamin A deficiency in intraperitoneal sclerosis induced by kieselguhr in rats, and found that there was no effect on the normal stages of histiogenesis of the intraperitoneal granulomas formed upon contact with the silica-containing substance. Daniel-Moussard (129) investigated the role of certain chelating agents, hoping that they would be found to "detoxify" the harmful silica-containing mineral particle. Disodium versenate, monocalcium versenate (ethylene-diamine tetracetate), B.A.L., (British Anti-Lewisite or 2-3-dimercaptopropanol), and Apresoline from CIBA, (1-hydrazinophthalazine chlorhydrate) were studied for their effect on rats treated with quartz of particle size 3 μ. In doses that were non-toxic to the animals none of the chelates had any effect on inhibiting silica fibrosis. In conclusion, Marks (331) studied 11 drugs, nine of them considered as histamine-releasing agents, while two were phenazines. The drugs were found to exert a protective effect on phagocytic cells in tissue culture against injury by silica dust, but the authors interpreted the effect as not associated with the histamine-releasing activity of the compounds. The phenazines also neutralized the toxicity of silica dust.

VI. Mechanism of Toxicity and the Factors Affecting It

The detailed mechanisms of silica toxicity were not fully described in any of the reports found. Silica can be absorbed by ingestion or by inhalation. When ingested, silica is acted upon by the stomach and intestines to form silicic acids and soluble silicate (380). Some silica is absorbed by the digestive tract and enters into the blood stream. One author states (511) that silica is generally assumed to circulate in the blood in the colloidal form. Accumulation occurs in varying degrees in some of the organs (084,511,273 and others) with excretion by the kidneys. A numerical estimate, made by Webb et al. (511) (on rats fed chronic doses), indicated excretion by the feces in the range of 95% of the dose administered, 4% in the urine, with 1% being accumulated in the tissues. When silica enters the body through the lungs a considerable amount is caught in the capillary bed of the lungs; while some progressively disappears with storage in other organs, a sizeable amount still remains (084 and others). The capillary bed of the lungs can also act as a filter for silica particles which have entered the blood

stream by other routes (359). Webb (511) states he does not find it surprising that the silica is picked up predominantly by organs containing a large amount of reticulo-endothelium tissue — i.e. liver and spleen.

Concerning acute toxicity, it was shown very early by Gye and Purdy (209) that massive intravascular clotting occurs in rabbits receiving i.v. injections of silicic acid (209). The authors pointed out that although this clotting was secondary to endothelial damage, it was the immediate cause of death. It was shown by Modell and Salzman (348), however, that even with administration of an anticoagulant, death occurred in cats given similar doses of silicic acid i.v. (See Table 4). Also the latter authors showed that there was no correlation between toxicity and either the acidity of the injected solution or the rate of injection. Others suggest that silicic acid exerts its toxic effect by constricting the blood vessels of the lung; and Filley, Hawley, and Wright (161) have described the specific bronchoconstriction produced by colloidal silica.

Much emphasis in the literature has been placed on particle size, and Dale and King have summarized the work of a number of experimentalists (124). They point out that it is well known that interstitial, intraperitoneal, and intratracheal injection of particulate silica produces only slow, chronic, silicotic fibrosis with no acute toxic reaction. On the other hand, both intratracheal and i.v. injections of finely divided silica of colloidal dimensions (20 A° or 2 mμ) into rats (16 mg per 250 g rat) produced rapid

shock-like death. Others obtained similar results with other animals (also see Table 4 this monograph). From their survey they concluded that the larger-sized particles (ca 0.1 to 10 μ) produce the slow chronic fibrogenic response of silicosis and no acute toxic effect, and that molecularly dispersed silicic acid is freely diffusible through animal tissues and membranes and is nontoxic and readily excreted by the kidney. The intensely toxic range then involves "colloidal size" particles. These authors themselves investigated a variety of dusts of different composition and particle size, and observed, for example, that colloidal silica is more than 10 times as toxic as quartz of larger dimensions. A number of substances of particle size 0.1 to 10 μ appeared to be rather similar in the amounts necessary to kill, but there was an apparent break between their required amounts and those for the 20 A°-particle-size silica.

In studies on quartz 6 μ, scotch whinstone 6 μ, flint <1 μ, silicic acid (a soluble silica), and precipitated silica given orally (521, see section 5, Metabolism and Excretion) it was noted that there was a definite increase of urinary silica from the flint, the precipitated silica, and, to a greater extent, from the silicic acid. If one considers urinary excretion as an indication of absorbtion and circulation in the blood stream with the possibility of accumulation and hence of tissue toxicity, it would seem that there is a correlation between toxicity and particle size indicated in these results.

Another example of the effect of silica of large particle size may be found in the work of Bertke (061, section 1 Short Term

Studies). Diatomaceous earth, of particle size range 640-0.46 μ with 55% <12 μ, when fed to rats 5% in their daily ration for 90 days caused no toxic symptoms. Nor was there any deviation from normal in histological sections or in silica content of the organs.

A pertinent study on particles of the colloidal range was that of Markovic and Arambasic (329)(section 3, Renal Mechanisms and Lesions) who induced chronic interstitial nephritis in guinea pigs by administering quartz of particle size 1-3 mμ, 250 mg/liter in drinking water for several months. Lesions were formed that were quite similar to those found in man in Yugoslavia -- an endemic nephropathy caused by rock erosion in village communitics on the banks of the lower reaches of large rivers.

Lundgren and Swensson (313) have pointed out, in regard to the pathogenesis of silicosis, that it is generally considered that quartz particles with a magnitude of 0.5 to 1 to 3 μ are of the greatest practical importance. They easily make their way down into the alveoli of the lungs and are retained there. Particles larger than 12 to 15 μ are to a large extent retained by the filtering apparatuses of the upper respiratory passages, and do not as frequently make their way down into the alveoli. Also, the fibrogenous effect of these larger particles seems less pronounced. To study the fibrogenesis of different particle sizes, the authors injected into guinea pigs in a single dose intraperitoneally somewhat coarse crystalline silica, 10 mg coarse particles of amorphous silica, and amorphous silica ca 61 mμ, ca 14 mμ. Large, coarse opaque

proliferative areas were seen in the peritoneum with cellular polymorphism and frequent infiltration of round cells. As particle size diminished, the proliferations of the peritoneum decreased in size.

For assessment of differences in toxicity between amorphous silicas of almost the same particle size, the work of Byers and Gage (084, Short Term Studies section 5) is of interest. The samples, from different suppliers, of particle size 19 mμ, 20 mμ (when fresh and 60 mμ later), and 25 mμ were administered intratracheally. As was pointed out earlier, silica was accumulated in the lungs and progressively disappeared, with some then appearing in the liver and kidneys. After 6 months, however, only the sample which showed evidence of aggregation (sample 2) was found in the latter organs. This sample had shown the greatest tendency to aggregate, when tested in a dust chamber; there was also greater difficulty in preparing aqueous suspensions.

A study considering surface area as well as particle size was that of Goldstein and Webster (201). These authors injected intratracheally into rats size-graded silica partles of <1 μ, 1 to 3 μ, and 2 to 5 μ; each group had a surface area of 600 sq. cm/ml. They found that the degree of fibrosis was greater for the two large size fractions, and on the basis of statistical analysis was apparently related to the quantity (by weight) of the silica injected or the particle size rather than to the surface area.

In one of the very few long-term studies that are available, Gardner and Cummings (176) administered quartz of size 1 to 3 μ,

and 6 to 12 μ, as well as aluminum oxide 1 to 3 μ, to rabbits by i.v. injection. (See Long Term Studies). After two to three years, histological examination showed that particles were segregated in different locations according to their size, the largest in the pulmonary capillaries, those of intermediate size in the spleen and hepatic lymph node, and the finest in the liver. The finest particles were the most active, while those of 10 to 12 μ were much less irritating, exciting a simple foreign body reaction which progressed little in three years. Fine aluminum oxide was merely phagocytosed and produced no fibrosis. This last study seems to indicate that the reaction, while correlated with particle size, is specific and chemical rather than purely physical in character (176).

Several authors have shown that polymerization and depolymerization of silicic acids may take place in various parts of the animal body. For example, Sauer, Laughland and Davidson (433, section 1, Guinea Pigs, Metabolism and Excretion) interpret their results as indicating that depolymerization of silica sol took place in the peritoneal cavity after oral administration. Arnold, Sasse and Strecker (041, Rats section 1, Metabolism and Excretion) after injecting i.p. aerosils of two different surface areas, and silicic acid gel, found that particles in the collecting tubules of the kidneys were essentially all the same size for the three different groups. From this they postulated polymerization in the distal nephron sections, a mechanism also proposed by others (041). Furthermore Settle and Sauer (445) postulated a critical concentration of 18 mg/100 ml of urine, below which soluble silica did

not polymerize.

Sauer et al. (433) found that solubility of the silica compound in the gastrointestinal tract is the limiting factor in its absorption. They also found that when guinea pigs were dosed with tetraethyl orthosilicate dissolved in 2.0 ml of ethanol, urinary excretion values were considerably higher than those for sodium silicate and silica sol mixed with the animals' food.

Different forms of silica of almost identical silica content, size distribution, and silica solubility were tested i.v. in mice, providing an example of the different results obtained according to chemical form (535). The fibrosing action in the liver was used as the criterion of measurement. It was found that tridymite was the most rapid in producing acellular collagenous silicotic nodules -- cristobalite was next, quartz third, and fused silica was the least fibrogenic. Silica particles were found initially in the spleen but with very little fibrosis. No fibrosis occurred in any other tissue. The authors proposed a mechanism possibly concerned with crystal structure and surface activity.

The study by Newberne and Wilson (372), already discussed in the sections on Short Term Studies and Metabolism and Excretion, serves as an example of the different results obtained from different silica salts. Sodium and magnesium silicates caused microscopic renal lesions in dogs, although no lesions were found in animals fed SiO_2 or aluminum silicate.

A theory proposed by Brieger and Gross (074) concerns the crystalline structure of silica necessary for fibrogenic

action. These authors studied coesite (particle size 0.14 μ) and quartz (particle size 0.44 μ); they gave intratracheal injections to rats and found that the fibrogenic potential of the two was of the same order. They concluded that the tetrahedral configuration of the SiO_2 molecule is a prerequisite for silicogenic action. This tetrahedral theory was substantiated by Strecker (470) in his study on the masking of SiO_2 surfaces. He prepared Aerosil surfaces which were masked with a number of agents, as illustrated in Table 29. When the Aerosil was administered to mice, these surface compounds delayed the acute toxic reaction, but not for long — as can be seen from the data in the table. He concluded that the reaction mechanism was connected with the free SiOH surface of solid particles constructed from SiO_2 tetrahedrons.

A final aspect to be considered when discussing the mechanism of toxicity is the action at the cellular level. Important works on the cytotoxic effects of silica compounds and the liberation of lysosomal enzymes have been published in England by Allison and Harington (216,012,010), and in Italy by Comolli (106). A detailed discussion of each is beyond the scope of this monograph, but attention is called to the concept, discussed by all of them and summarized so clearly by Allison (012). It is that silica particles are toxic because they are efficiently taken up by macrophages, and can then react realtively rapidly with the membranes surrounding the secondary lysosomes. The particles and lytic enzymes then can escape into the cytoplasm, causing general damage. Allison suggests that hydrogen bonding of silicic acid with lipid and protein constituents

of the membrane accounts for the induced permeability. Silica released from killed macrophages is as cytotoxic as the original preparation, and it is suggested that repeated cycles of macrophage killing in vivo leads to the mobilization of fibroblasts and fibrogenesis characterizing the disease silicosis.

Table 29 (470)

Masking of Aerosil Surfaces

Std. = Hours Tg. = Days

Aerosil surface		Dose in mg	Death rate
Si-Oberfläche		Dosis: mg	Todesrate
≡Si-OH		20	100% in 48 Std.
≡Si-O-C-C-OH	●	20	100% nach 48 Std
≡Si-O-C-C-H	●	30	90% in 10 Tg.
		60	100% in 3 Tg.
≡Si-O-C-C-C-C-H	●	30	~50% in 14 Tg.
		60	
Si-O-C-C-C-C-C-C-C-C-H	●	30	~30% in 14 Tg.
		60	
≡Si-O-C-C-C-C-H	◑	20	—o—
		40	10% in 14 Tg.
	◔	20	30% in 3 Tg.
		40	50% in 3 Tg. 80% in 14 Tg.
≡Si-O-Si(CH3)(CH3)-CH3	●	60	—o—
	◑	60	—o—
≡Si-O-Al(OH)-OH	●	30	20% in 60 Std.
		60	40% in 60 Std.

Ill. 1: Toxicity of aerosil with various surface coverings. (Fatalities in mice with intraperitoneal application.)

VII. Consumer Exposure Information

The consumer may be exposed to silica from numerous natural and environmental sources, as discussed in the section on Chemical Information. The FDA has issued regulations for the use of calcium silicate (020,021) and sodium aluminosilicate (018,019) as anticaking agents; they specify a maximum usage of 2%, in salt for the former chemical and dried eggs for the latter. It has regulated silicon dioxide (016) to be used as an anticaking agent in vitamin products, 0.5%; in special dietary products, 0.75%; in spices, 2%; in meat-curing compounds, 2%; and in flavoring powders, 2%. A further regulation (025) extends the use of SiO_2 as an anticaking agent to any food at a maximum level of 2% when it has been demonstrated to have the anticaking effect; it is to be used at 2% in baby foods, however, only if NaCl, or NaCl substitutes, is a component.

The WHO/FAO monograph on "Toxicological Evaluation of Some Food Colors, Emulsifiers, Stabilizers, and Anti-Caking Agents and Certain Other Substances", 1969, (165), set no limit on Acceptable Daily Intakes (ADI) for the various forms of silicon dioxide, aluminum silicate, calcium silicate, magnesium silicate (including talc) and sodium alumino silicate.

The NAS/NRC GRAS Survey Report lists the values shown in Table 30 for usage levels of four silica compounds in regular foods. Also, the Survey tabulates the possible daily intake per food category and total dietary level, based on the food consumption by total

Table 30

NAS/NRC GRAS Survey Report for Usage Levels of Silica Compounds in Foods

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO.	NAME	# FIRMS REPORTING	*** USUAL USE *** WTD MEAN, %	*** MAXIMUM USE *** WTD MEAN, %
CALCIUM SILICATE	01	BAKED GOODS(R)	*	.15500	.15500
NAS 0055	03	OTHER GRAIN(R)	*	.05440	.05440
	04	FATS OILS(R)	*	.19200	.19200
	10	MEAT PRODS(R)	4	.00980	.01950
	11	POULTRY(R)	*	.00691	.01111
	13	FISH PRODS(R)	*	.01700	.01700
	16	SOFT CANDY(R)	*	.01024	.01883
	21	SOUPS(R)	4	.03163	.03187
	22	SNACK FOODS(R)	4	.12843	.57733
	23	DEV TYPE I(R)	*	.00070	.00200
	25	NUT PRODS(R)	*	.00564	.01055
	27	GRAVIES(R)	*	.03322	.06562
	28	IMIT DAIRY(R)	*	.49330	.49330
	48	SEAS FLAVRS(R)	*	.30167	.70094
SILICA AEROGEL	01	BAKED GOODS(R)	*	.03226	.04935
NAS 0174 FEMA 3506	02	BREAK CERLS(R)	*	.00850	.00850
	03	OTHER GRAIN(R)	*	.07500	.07500
	05	MILK PRODS(R)	*	.04997	.05297
	10	MEAT PRODS(R)	*	.00764	.01975
	11	POULTRY(R)	*	.01000	.05000
	13	FISH PRODS(R)	*	.01000	.05000
	21	SOUPS(R)	5	.01969	.02183
	22	SNACK FOODS(R)	*	.00100	.00500
	23	DEV TYPE I(R)	*	.04300	.04300
	27	GRAVIES(R)	*	.05045	.10050
	30	HARD CANDY(R)	*	.00750	.00750
	48	SEAS FLAVRS(R)	*	.40644	.40644
SODIUM ALUMINOSILICATE	01	BAKED GOODS(R)	*	.68039	1.39242
NAS 0178	02	BREAK CERLS(R)	*	.00015	.00045
	03	OTHER GRAIN(R)	*	.03600	.03600
	04	FATS OILS(R)	*	.04000	.06000
	05	MILK PRODS(R)	*	.03848	.03975
	07	FROZN DAIRY(R)	*	.00299	.00498
	10	MEAT PRODS(R)	*	.00014	.00047
	11	POULTRY(R)	*	.01000	.05000
	13	FISH PRODS(R)	*	.00100	.00100
	15	CONDN RELSH(R)	*	.17217	.34435
SODIUM ALUMINOSILICATE (CONT.)	19	SWEET SAUCE(R)	*	.30675	.30675
NAS 0178	20	GELATIN PUD(R)	*	.03000	.07000
	21	SOUPS(R)	4	.41959	.42044
	22	SNACK FOODS(R)	*	.83145	.92760
	23	DEV TYPE I(R)	*	.07919	.07910
	27	GRAVIES(R)	*	.06434	.19911
	28	IMIT DAIRY(R)	5	.87533	.87533
	48	SEAS FLAVRS(R)	*	.53930	.53950

sample, as shown in Table 31. In summary, the GRAS survey reports a high possible daily intake of calcium silicate for the 2-65 year old age group as ca 481 mg; for silica aerogel ca 340 mg, for sodium aluminum silicate ca 2278 mg and for sodium calcium aluminosilicate hydrate 2.66 mg.

The annual poundage data for calcium silicate, magnesium silicate and silica aerogel is reported in Table 32.

Table 31

Possible Daily Intakes of NAS Appendix A Substances (Groups I & II), Per Food Category and Total Dietary, Based on Food Consumption by Total Sample --- See Explanatory Notes in Exhibits Section

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO.	NAME	# FIRMS REPORTING	*** USUAL USE *** WTD MEAN, %	*** MAXIMUM USE *** WTD MEAN, %
CALCIUM SILICATE	01	BAKED GOODS(R)	*	.15500	.15500
NAS 0055	03	OTHER GRAIN(R)	*	.05440	.05440
	04	FATS OILS(R)	*	.19200	.19200
	10	MEAT PRODS(R)	4	.00980	.01950
	11	POULTRY(R)	*	.00691	.01111
	13	FISH PRODS(R)	*	.01700	.01700
	16	SOFT CANDY(R)	*	.01024	.01883
	21	SOUPS(R)	4	.03163	.03187
	22	SNACK FOODS(R)	4	.12843	.57733
	23	BEV TYPE I(R)	*	.00070	.00200
	25	NUT PRODS(R)	*	.00564	.01055
	27	GRAVIES(R)	*	.03322	.06562
	28	IMIT DAIRY(R)	*	.49330	.49330
	48	SEAS FLAVRS(R)	*	.30167	.70094
SILICA AEROGEL	01	BAKED GOODS(R)	*	.03226	.04935
NAS 0174 FEMA 3506	02	BREAK CERLS(R)	*	.00850	.00850
	03	OTHER GRAIN(R)	*	.07500	.07500
	05	MILK PRODS(R)	*	.04997	.05297
	10	MEAT PRODS(R)	*	.00764	.01973
	11	POULTRY(R)	*	.01000	.05000
	13	FISH PRODS(R)	*	.01000	.05000
	21	SOUPS(R)	5	.01969	.02183
	22	SNACK FOODS(R)	*	.00100	.00500
	23	BEV TYPE I(R)	*	.04300	.04300
	27	GRAVIES(R)	*	.05045	.10050
	30	HARD CANDY(R)	*	.00750	.00750
	48	SEAS FLAVRS(R)	*	.40644	.40644
SODIUM ALUMINOSILICATE	01	BAKED GOODS(R)	*	.68039	1.39242
NAS 0178	02	BREAK CERLS(R)	*	.00015	.00045
	03	OTHER GRAIN(R)	*	.03400	.03400
	04	FATS OILS(R)	*	.04000	.06000
	05	MILK PRODS(R)	*	.03848	.03975
	07	FROZN DAIRY(R)	*	.00299	.00498
	10	MEAT PRODS(R)	*	.00014	.00047
	11	POULTRY(R)	*	.01000	.05000
	13	FISH PRODS(R)	*	.00100	.00100
	15	CONDM RELSH(R)	*	.17217	.34435
SODIUM ALUMINOSILICATE (CONT.)	19	SWEET SAUCE(R)	*	.38675	.38675
NAS 0178	20	GELATIN PUD(R)	*	.03000	.07000
	21	SOUPS(R)	4	.41969	.42044
	22	SNACK FOODS(R)	*	.83145	.92768
	23	BEV TYPE I(R)	*	.07918	.07918
	27	GRAVIES(R)	*	.06434	.19911
	28	IMIT DAIRY(R)	5	.87533	.87533
	48	SEAS FLAVRS(R)	*	.53938	.53950

Table 31

Possible Daily Intakes of NAS Appendix A Substances (Groups I & II). Per Food Category and Total Dietary, Based on Food Consumption by Total Sample --- See Explanatory Notes in Exhibits Section

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO. NAME	# OF FIRMS	(AGE)	POSSIBLE DAILY INTAKE, MG. AVERAGE	HIGH A	HIGH B
CALCIUM SILICATE NAS 0055	01 BAKED GOODS(R)	*	0-5 MO.	5.270000	6.975000	5.270000
			6-11 MO.	39.370000	80.290000	39.370000
			12-23 MO.	84.475000	139.190000	84.475000
			2-65+ YR.	212.660000	315.890000	212.660000
CALCIUM SILICATE NAS 0055	03 OTHER GRAIN(R)	*	0-5 MO.	.272000	.924800	.272000
			6-11 MO.	5.276800	15.558400	5.276800
			12-23 MO.	8.921600	20.617600	8.921600
			2-65+ YR.	15.123200	33.401600	15.123200
CALCIUM SILICATE NAS 0055	04 FATS OILS(R)	*	0-5 MO.	.960000	.960000	.960000
			6-11 MO.	5.376000	14.400000	5.376000
			12-23 MO.	12.096000	23.040000	12.096000
			2-65+ YR.	33.600000	60.672000	33.600000
CALCIUM SILICATE NAS 0055	10 MEAT PRODS(R)	4	0-5 MO.	.107800	.284200	.214500
			6-11 MO.	2.028600	5.468400	4.036500
			12-23 MO.	2.959600	5.086200	5.885000
			2-65+ YR.	7.683200	12.749800	15.288000
CALCIUM SILICATE NAS 0055	11 POULTRY(R)	*	0-5 MO.	.034550	.150930	.055550
			6-11 MO.	.269490	.912120	.433290
			12-23 MO.	.456060	1.271440	.733260
			2-65+ YR.	.891390	2.266480	1.433190
CALCIUM SILICATE NAS 0055	13 FISH PRODS(R)	*	0-5 MO.	.017000	.051000	.017000
			6-11 MO.	.221000	.833000	.221000
			12-23 MO.	.918000	2.295000	.918000
			2-65+ YR.	2.108000	5.253000	2.108000
CALCIUM SILICATE NAS 0055	16 SOFT CANDY(R)	*	0-5 MO.	.020480	.204800	.037660
			6-11 MO.	.225280	.696320	.414260
			12-23 MO.	.358400	.952320	.659050
			2-65+ YR.	.593920	1.802240	1.092140
CALCIUM SILICATE NAS 0055	21 SOUPS(R)	4	0-5 MO.	.063260	.474450	.063740
			6-11 MO.	7.369790	22.995010	7.425710
			12-23 MO.	11.007240	30.396430	11.090760
			2-65+ YR.	10.026710	26.727350	10.102790
CALCIUM SILICATE NAS 0055	22 SNACK FOODS(R)	4	0-5 MO.	**********	.128430	**********
			6-11 MO.	.513720	1.412730	2.309320
			12-23 MO.	1.412730	3.981330	6.350630
			2-65+ YR.	1.669550	4.751910	7.505290
CALCIUM SILICATE NAS 0055	23 BEV TYPE I(R)	*	0-5 MO.	.016800	.025200	.048000
			6-11 MO.	.158900	.543900	.454000
			12-23 MO.	.379400	1.137500	1.084000
			2-65+ YR.	.728000	1.943900	2.080000

Table 31

Possible Daily Intakes of NAS Appendix A Substances (Groups I & II), Per Food Category and Total Dietary, Based on Food Consumption by Total Sample --- See Explanatory Notes in Exhibits Section

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO. NAME	# OF FIRMS	(AGE)	POSSIBLE DAILY INTAKE, MG. AVERAGE	HIGH A	HIGH B
CALCIUM SILICATE NAS 0055	25 NUT PRODS(R)	*	0-5 MO.	**********	.011280	**********
			6-11 MO.	.208660	.755760	.390350
			12-23 MO.	.152280	.507600	.284850
			2-65+ YR.	.293200	.874200	.548600
CALCIUM SILICATE NAS 0055	27 GRAVIES(R)	*	0-5 MO.	.033220	.099660	.065620
			6-11 MO.	.465080	1.295500	.918680
			12-23 MO.	1.195920	3.388440	2.362320
			2-65+ YR.	2.757260	7.075860	5.446460
CALCIUM SILICATE NAS 0055	28 IMIT DAIRY(R)	*	0-5 MO.	.000000	.000000	.000000
			6-11 MO.	6.906200	11.345900	6.906200
			12-23 MO.	3.946400	16.772200	3.946400
			2-65+ YR.	4.439700	7.399500	4.439700
CALCIUM SILICATE NAS 0055	43 SEAS FLAVRS(R)	*	0-5 MO.	**********	**********	**********
			6-11 MO.	**********	.030167	**********
			12-23 MO.	**********	.060334	**********
			2-65+ YR.	.030167	.150835	.070094
CALCIUM SILICATE NAS 0055	ALL CATEGORIES ********** ********** **********	13	0-5 MO.	6.795110	10.297750	7.004070
			6-11 MO.	68.389540	156.537287	73.532110
			12-23 MO.	128.278630	248.696394	138.810870
			2-65+ YR.	292.604417	480.958675	311.497464
SILICA AEROGEL NAS 0174	01 BAKED GOODS(R)	*	0-5 MO.	1.096840	1.451700	1.677900
			6-11 MO.	8.194040	16.710680	12.534900
			12-23 MO.	17.581700	28.969480	26.895750
			2-65+ YR.	44.260720	65.745880	67.708200
SILICA AEROGEL NAS 0174	02 .BREAK CERLS(R)	*	0-5 MO.	.051000	.144500	.051000
			6-11 MO.	1.895500	5.083000	1.895500
			12-23 MO.	2.218500	4.326500	2.218500
			2-65+ YR.	1.700000	4.403000	1.700000
SILICA AEROGEL NAS 0174	03 OTHER GRAIN(R)	*	0-5 MO.	.375000	1.275000	.375000
			6-11 MO.	7.275000	21.450000	7.275000
			12-23 MO.	12.300000	28.425000	12.300000
			2-65+ YR.	20.850000	46.050000	20.850000
SILICA AEROGEL NAS 0174	05 MILK PRODS(R)	*	0-5 MO.	2.698380	1.998800	2.860380
			6-11 MO.	31.181280	145.959970	33.053280
			12-23 MO.	27.233050	87.147680	28.866650
			2-65+ YR.	19.738150	60.263820	20.923150

Table 31

Possible Daily Intakes of NAS Appendix A Substances (Groups I & II), Per Food Category and Total Dietary, Based on Food Consumption by Total Sample --- See Explanatory Notes in Exhibits Section

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO.	NAME	# OF FIRMS	(AGE)	POSSIBLE DAILY INTAKE, MG. AVERAGE	HIGH A	HIGH B
SILICA AEROGEL NAS 0174	10	MEAT PRODS(R)	*	0-5 MO.	.004040	.221560	.217030
				6-11 MO.	1.581480	4.263120	4.084110
				12-23 MO.	2.307280	3.965160	5.958460
				2-65+ YR.	5.989760	9.939640	15.466320
SILICA AEROGEL NAS 0174	11	POULTRY(R)	*	0-5 MO.	.050000	.230000	.250000
				6-11 MO.	.390000	1.320000	1.950000
				12-23 MO.	.660000	1.840000	3.300000
SILICA AEROGEL NAS 0174	13	FISH PRODS(R)	*	0-5 MO.	.010000	.030000	.050000
				6-11 MO.	.130000	.490000	.650000
				12-23 MO.	.540000	1.350000	2.700000
				2-65+ YR.	1.240000	3.090000	6.200000
SILICA AEROGEL NAS 0174	21	SOUPS(R)	5	0-5 MO.	.039300	.295350	.043660
				6-11 MO.	4.587770	14.314630	5.086390
				12-23 MO.	6.852120	18.922090	7.596840
				2-65+ YR.	6.241730	16.638050	6.920110
SILICA AEROGEL NAS 0174	22	SNACK FOODS(R)	*	0-5 MO.	**********	.001000	**********
				6-11 MO.	.004000	.011000	.020000
				12-23 MO.	.011000	.031000	.055000
				2-65+ YR.	.013000	.037000	.065000
SILICA AEROGEL NAS 0174	23	BEV TYPE I(R)	*	0-5 MO.	1.032000	1.548000	1.032000
				6-11 MO.	9.761000	33.411000	9.761000
				12-23 MO.	23.306000	69.879000	23.306000
				2-65+ YR.	44.720000	119.411000	44.720000
SILICA AEROGEL NAS 0174	27	GRAVIES(R)	*	0-5 MO.	.050450	.151350	.100500
				6-11 MO.	.706300	1.967550	1.407000
				12-23 MO.	1.816200	5.145900	3.618000
				2-65+ YR.	4.187350	10.745850	8.341500
SILICA AEROGEL NAS 0174	30	HARD CANDY(R)	*	0-5 MO.	.000000	.000000	.000000
				6-11 MO.	.007500	.022500	.007500
				12-23 MO.	.022500	.067500	.022500
				2-65+ YR.	.045000	.127500	.045000
SILICA AEROGEL NAS 0174	48	SEAS FLAVRS(R)	*	0-5 MO.	**********	**********	**********
				6-11 MO.	**********	.040644	**********
				12-23 MO.	**********	.081288	**********
				2-65+ YR.	.040644	.203220	.040644
SILICA AEROGEL NAS 0174	ALL CATEGORIES		16	0-5 MO.	5.487090	7.347260	6.657470
	**********			6-11 MO.	65.713070	249.044094	77.724680
	**********			12-23 MO.	94.648950	250.146598	116.839700
	**********			2-65+ YR.	150.316354	335.934960	199.431924

Table 31

Possible Daily Intakes of NAS Appendix A Substances (Groups I & II), Per Food Category and Total Dietary, Based on Food Consumption by Total Sample --- See Explanatory Notes in Exhibits Section

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO.	NAME	# OF FIRMS	(AGE)	POSSIBLE DAILY INTAKE, MG. AVERAGE	HIGH A	HIGH B
SODIUM ALUMINOSILICATE NAS 0178	01	BAKED GOODS(R)	*	0-5 MO.	23.133260	30.617550	47.342260
				6-11 MO.	172.819060	352.442020	353.674680
				12-23 MO.	370.812550	610.990220	758.868900
				2-65+ YR.	933.495080	1386.634820	1910.400240
SODIUM ALUMINOSILICATE NAS 0178	02	BREAK CERLS(R)	*	0-5 MO.	.000900	.002550	.002700
				6-11 MO.	.033450	.089700	.100350
				12-23 MO.	.039150	.076350	.117450
				2-65+ YR.	.030000	.077700	.090000
SODIUM ALUMINOSILICATE NAS 0178	03	OTHER GRAIN(R)	*	0-5 MO.	.180000	.612000	.180000
				6-11 MO.	3.492000	10.296000	3.492000
				12-23 MO.	5.904000	13.644000	5.904000
				2-65+ YR.	10.008000	22.104000	10.008000
SODIUM ALUMINOSILICATE NAS 0178	04	FATS OILS(R)	*	0-5 MO.	.200000	.200000	.300000
				6-11 MO.	1.120000	3.000000	1.680000
				12-23 MO.	2.520000	4.800000	3.780000
				2-65+ YR.	7.000000	12.640000	10.500000
SODIUM ALUMINOSILICATE NAS 0178	05	MILK PRODS(R)	*	0-5 MO.	2.077920	1.539200	2.146500
				6-11 MO.	24.011520	115.478480	24.804000
				12-23 MO.	20.971600	67.109120	21.663750
				2-65+ YR.	15.199600	46.406880	15.701250
SODIUM ALUMINOSILICATE NAS 0178	07	FRCZN DAIRY(R)	*	0-5 MO.	.029900	.122590	.045800
				6-11 MO.	.284050	.789360	.473100
				12-23 MO.	.430960	1.010620	.717120
				2-65+ YR.	.765440	1.844830	1.274880
SODIUM ALUMINOSILICATE NAS 0178	10	MEAT PRODS(R)	*	0-5 MO.	.001540	.004060	.005170
				6-11 MO.	.026980	.078120	.097250
				12-23 MO.	.042280	.072660	.141940
				2-65+ YR.	.109760	.182140	.366480
SODIUM ALUMINOSILICATE NAS 0178	11	POULTRY(R)	*	0-5 MO.	.090000	.230000	.250000
				6-11 MO.	.390000	1.320000	1.650000
				12-23 MO.	.660000	1.840000	3.300000
				2-65+ YR.	1.290000	3.280000	6.450000
SODIUM ALUMINOSILICATE NAS 0178	13	FISH PRODS(R)	*	0-5 MO.	.001000	.003000	.001000
				6-11 MO.	.013000	.049000	.013000
				12-23 MO.	.054000	.135000	.054000
				2-65+ YR.	.124000	.309000	.124000
SODIUM ALUMINOSILICATE NAS 0178	15	COOKM RELSH(R)	*	0-5 MO.	**********	.172170	**********
				6-11 MO.	1.377360	3.797740	2.754800
				12-23 MO.	4.820750	13.084920	9.641800
				2-65+ YR.	15.150960	36.500040	30.302800

Table 31

Possible Daily Intakes of NAS Appendix A Substances (Groups I & II). Per Food Category and Total Dietary, Based on Food Consumption by Total Sample --- See Explanatory Notes in Exhibits Section

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO.	NAME	# OF FIRMS	(AGE)	POSSIBLE DAILY INTAKE, MG. AVERAGE	HIGH A	HIGH B
SODIUM ALUMINOSILICATE NAS 0178	19	SWEET SAUCE(R)	*	0-5 MO.	1.160250	1.547000	1.160250
				6-11 MO.	3.480750	11.989250	3.480750
				12-23 MO.	10.055500	29.393000	10.055500
				2-65+ YR.	26.299000	69.228250	26.299000
SODIUM ALUMINOSILICATE NAS 0178	20	GELATIN PUD(R)	*	0-5 MO.	.600000	.810000	1.400000
				6-11 MO.	3.840000	11.640000	8.960000
				12-23 MO.	4.140000	10.080000	9.660000
				2-65+ YR.	6.120000	15.750000	14.280000
SODIUM ALUMINOSILICATE NAS 0178	21	SOUPS(R)	4	0-5 MO.	.839380	6.295350	.840880
				6-11 MO.	97.767770	305.114630	97.962520
				12-23 MO.	146.052120	403.222090	146.313120
				2-65+ YR.	133.041730	354.638050	133.279480
SODIUM ALUMINOSILICATE NAS 0178	22	SNACK FOODS(R)	*	0-5 MO.	**********	.631450	**********
				6-11 MO.	2.525800	6.945950	3.710720
				12-23 MO.	6.945950	19.574950	10.204480
				2-65+ YR.	8.208850	23.363650	12.059840
SODIUM ALUMINOSILICATE NAS 0178	23	BEV TYPE I(R)	*	0-5 MO.	1.900320	2.850480	1.900320
				6-11 MO.	17.973860	61.522860	17.973860
				12-23 MO.	42.915560	128.667500	42.915560
				2-65+ YR.	82.347200	219.892960	82.347200
SODIUM ALUMINOSILICATE NAS 0178	27	GRAVIES(R)	*	0-5 MO.	.064340	.193020	.199110
				6-11 MO.	.900760	2.509260	2.787540
				12-23 MO.	2.316240	6.582680	7.167960
				2-65+ YR.	5.340220	13.704420	16.526130
SODIUM ALUMINOSILICATE NAS 0178	28	IMIT DAIRY(R)	5	0-5 MO.	.000000	.000000	.000000
				6-11 MO.	12.254620	20.132590	12.254620
				12-23 MO.	7.002640	29.761220	7.002640
				2-65+ YR.	7.877970	13.129950	7.877970
SODIUM ALUMINOSILICATE NAS 0178	48	SEAS FLAVRS(R)	*	0-5 MO.	**********	**********	**********
				6-11 MO.	**********	.053938	**********
				12-23 MO.	**********	.107876	**********
				2-65+ YR.	.053938	.269690	.053950
SODIUM ALUMINOSILICATE NAS 0178	ALL CATEGORIES	**********	20	0-5 MO.	30.230210	45.830420	55.770010
		**********		6-11 MO.	342.339590	907.239890	536.169230
		**********		12-23 MO.	625.692910	1340.232206	1037.508220
		**********		2-65+ YR.	1252.461748	2219.946280	2277.943220

Table 31

Possible Daily Intakes of NAS Appendix A Substances (Groups I & II), Per Food Category and Total Dietary, Based on Food Consumption by Total Sample --- See Explanatory Notes in Exhibits Section

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO. NAME	# OF FIRMS	(AGE)	POSSIBLE DAILY INTAKE, MG. AVERAGE	HIGH A	HIGH B
SODIUM CAL ALUMSIL HYD NAS 0184	10 MEAT PRODS(R)	*	0-5 MO.	.011000	.029000	.055000
			6-11 MO.	.207000	.558000	1.035000
			12-23 MO.	.302000	.519000	1.510000
			2-65+ YR.	.784000	1.301000	3.920000
SODIUM CAL ALUMSIL HYD NAS 0184	11 POULTRY(R)	*	0-5 MO.	.005000	.023000	.025000
			6-11 MO.	.039000	.132000	.195000
			12-23 MO.	.066000	.184000	.330000
			2-65+ YR.	.129000	.328000	.645000
SODIUM CAL ALUMSIL HYD NAS 0184	21 SOUPS(R)	*	0-5 MO.	.002000	.015000	.010000
			6-11 MO.	.233000	.727000	1.165000
			12-23 MO.	.348000	.961000	1.740000
			2-65+ YR.	.317000	.845000	1.585000
SODIUM CAL ALUMSIL HYD NAS 0184	22 SNACK FOODS(R)	*	0-5 MO.	**********	.005000	**********
			6-11 MO.	.020000	.055000	.040000
			12-23 MO.	.055000	.155000	.110000
			2-65+ YR.	.065000	.185000	.130000
SODIUM CAL ALUMSIL HYD NAS 0184	ALL CATEGORIES ********** ********** **********	*	0-5 MO.	.018000	.072000	.090000
			6-11 MO.	.499000	1.472000	2.435000
			12-23 MO.	.771000	1.819000	3.690000
			2-65+ YR.	1.295000	2.659000	6.280000

Table 32 Animal Poundage Data for NAS Appendix A

	Reports to NAS 1960/70	1960	1970	Total 1970 Poundage to NAS	Poundage to FEMA	NAS + FEMA
Calcium Silicate	13/15	1,012,650	1,154,391	1,290,466		1,290,466
Magnesium Silicate	5/5	52,175	47,144	47,144		47,144
Silica Aerogel	14/16	66	23,277	29,627	6,666	36,293

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